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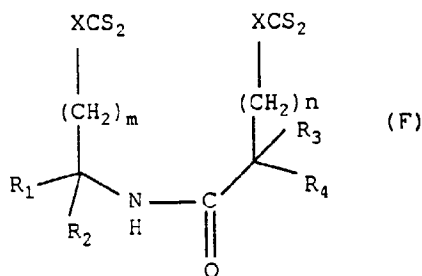
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(54) Title: COMPOUND FOR CHELATING A METAL, RADIOPHARMACEUTICAL, MANUFACTURING PROCESS THEREFOR, AND DIAGNOSTIC KIT



(57) Abstract: The present invention provides a compound for chelating a metal or a metal complex, characterized in that it consists of a bis-dithiocarbamate structure (F) having the formula below: (formule chimique à insérer ici) in which n and m are integers such that 5 < m+n < 10, X is chosen independently from S and NH, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are chosen independently from H and an organic function chosen from -COOR<sub>5</sub>, NR<sub>5</sub>R<sub>6</sub> and -CH<sub>2</sub>OR<sub>5</sub> in which R<sub>5</sub> and R<sub>6</sub>, when it is present, are chosen independently from a hydrogen; an amino acid; a peptide; a protein; monoclonal antibody; a hormone; and a pharmaceutically acceptable vector. The present invention also provides a diagnostic kit comprising a chelating compound according to the present invention.

**COMPOUND FOR CHELATING A METAL, RADIOPHARMACEUTICAL,  
MANUFACTURING PROCESS THEREFOR, AND DIAGNOSTIC KIT**

**DESCRIPTION**

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**Technical field of the invention**

The present invention relates to a compound for chelating a metal or a metal complex, to a radiopharmaceutical, to a manufacturing process thereof and to a diagnostic kit.

The chelation compound may be used to manufacture a diagnostic product or a medicinal product.

The metal may be a transition metal chosen, for example, from Tc, Ru, Co, Cu, Pt, Fe, Os, Ir, Re, Cr, Mo, Mn, Ni, Rh, Pd, Nb, Sm and Ta or an isotope thereof.

The metal complex may be, for example, a nitride complex of radioactive transition metals which may be used as radiopharmaceutical products for diagnosis or therapy.

Among the complexes which may be used for diagnosis, mention may be made in particular of technetium <sup>99m</sup>Tc complexes.

Radiopharmaceutical products using the <sup>99m</sup>Tc radionuclide are very useful in nuclear medicine for diagnosis on account of its physical and chemical characteristics. Technetium complexes which may be used for the present invention are described, for example, by E. DEUTSCH et al. in: Progr. Inorg. Chem. (Australia), vol. 30, pp. 76-106, 1983, and preparation processes are described in J. Baldas et al. in J. Chem. Soc. Dalton Trans 1981, pp. 1798-1801; in Int. Appl.

Radiot. Isot. 36 (1985), pp. 133-139, in international patent application WO 85/03063. and in patent applications EP-A-537 242 and EP-A-0 403 524.

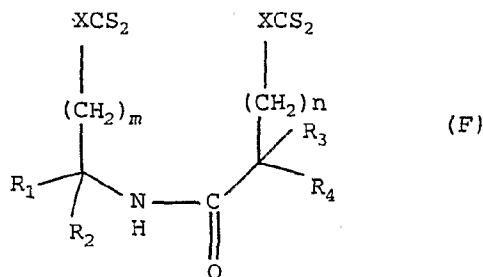
The complexes which may be used for therapy may be, for example, rhenium complexes.

Copper or an isotope thereof is useful for the present invention, for example for labelling antibodies or peptides, for diagnosis and especially for therapy ( $^{67}\text{Cu}$ ,  $^{64}\text{Cu}$ ).

10

### Description of the invention

The compound for chelating a metal or a metal complex of the present invention is characterized in that it consists of a bis-dithiocarbamate structure (F) having the following formula:



in which n and m are integers such that  $5 \leq m+n \leq 10$ ,

X is chosen independently from S and NH,

$\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $\text{R}_4$  are chosen independently from H and an organic function chosen from  $-\text{COOR}_5$ ,  $\text{NR}_5\text{R}_6$  and  $-\text{CH}_2\text{OR}_5$  in which  $\text{R}_5$  and  $\text{R}_6$ , when it is present, are chosen independently from a hydrogen; an amino acid; a peptide; a protein; an organic function; a group chosen from alkoxycarbonyl or aryloxycarbonyl ( $-\text{COOR}^7$ ), carboxyl ( $-\text{COOH}$ ), acyloxy ( $-\text{O}_2\text{R}^7$ ), carbamoyl ( $-\text{CONR}^7$ ), cyano ( $-\text{CN}$ ), alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, arylalkylcarbonyl, hydroxyl ( $-\text{OH}$ ), amino

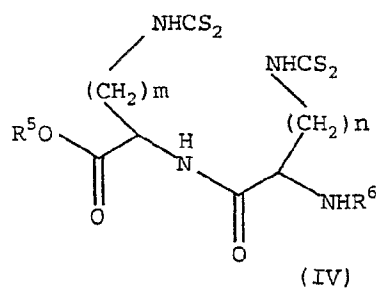
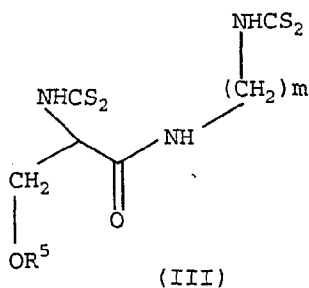
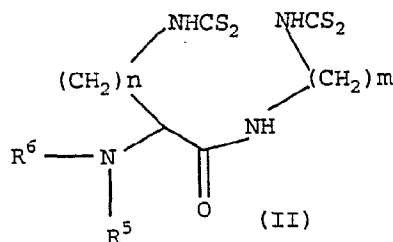
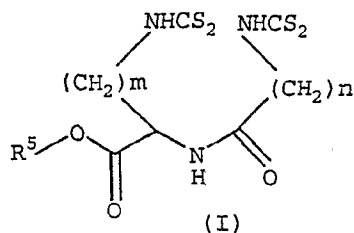
(NR<sup>7</sup>), halogen, allyl, alkoxy (-OR<sup>7</sup>), S-alkyl and S-aryl, R<sup>7</sup> representing a C<sub>1</sub> to C<sub>10</sub> alkyl or aryl group; an organic molecule chosen from (i) an optionally substituted alkyl, acyl, aryl or alkyne group, (ii) a  
5 saturated or unsaturated, optionally substituted or aromatic carbon-based ring or (iii) a saturated or unsaturated, optionally substituted or aromatic heterocycle, these groups and rings (i), (ii) and (iii) possibly being substituted with substituted phenyl  
10 groups, substituted aromatic groups or alkoxycarbonyl or aryloxycarbonyl (-COOR<sup>8</sup>), carboxyl (-COOH), acyloxy (-O<sub>2</sub>R<sup>8</sup>), carbamoyl (-CONR<sup>8</sup>), alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, arylalkylcarbonyl, hydroxyl (-OH), amino (NR<sup>8</sup>), halogen, allyl, alkoxy  
15 (-OR<sup>8</sup>), S-alkyl or S-aryl groups, R<sup>8</sup> representing a C<sub>1</sub> to C<sub>10</sub> alkyl or aryl group; a monoclonal antibody; a hormone; and a pharmaceutically acceptable vector.

n and m are natural integers. Thus, m and n may be, independently, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10,  
20 provided that  $5 \leq m+n \leq 10$ . For example, for m=0, n may be 5, 6, 7, 8, 9 or 10, and for m=1, n may be 4, 5, 6, 7, 8 or 9. According to the invention, the functions XCS<sub>2</sub> are in fact separated by a peptide bond and a number of carbon atoms greater than or equal to 7 and less than  
25 or equal to 10.

The present invention provides a novel system for complexing a metal or a metal complex which may be linked to any molecule or biomolecule. This system thus has numerous applications, especially for diagnosis and  
30 therapy.

According to the invention, the bis-dithio-carbamate compound may consist of a structure whose formula is chosen from formulae (I), (II), (III) and (IV) below:

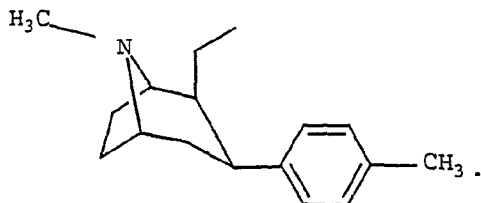
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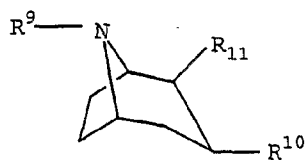
in which n and R<sup>5</sup>, and m and R<sup>6</sup>, when they are present, are as defined above.

According to the invention, R<sup>5</sup> may be chosen from  
15 H, CH<sub>3</sub>, a tropane derivative or a compound of formula:



When R<sup>5</sup> is a tropane derivative, it may be of formula (G) below:

5

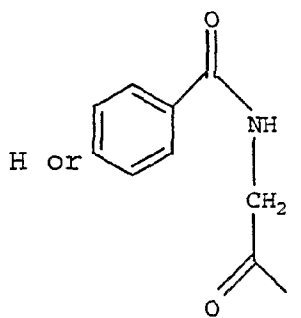


(G)

in which one of the radicals  $R^9$ ,  $R^{10}$  and  $R^{11}$  is a compound of formula F, the other radicals being chosen independently from a hydrogen; an organic function; a group chosen from alkoxycarbonyl or aryloxycarbonyl (-COOR<sup>7</sup>), carboxyl (-COOH), acyloxy (-O<sub>2</sub>R<sup>7</sup>), carbamoyl (-CONR<sup>7</sup>), cyano (-CN), alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, arylalkylcarbonyl, hydroxyl (-OH), amino (NR<sup>7</sup>), halogen, allyl, alkoxy (-OR<sup>7</sup>), S-alkyl and S-aryl, R<sup>7</sup> representing a C<sub>1</sub> to C<sub>10</sub> alkyl or aryl group; an organic molecule chosen from (i) an optionally substituted alkyl, acyl, aryl or alkyne group, (ii) a saturated or unsaturated, optionally substituted or aromatic carbon-based ring or (iii) a saturated or unsaturated, optionally substituted or aromatic heterocycle, these groups and rings (i), (ii) and (iii) possibly being substituted with substituted phenyl groups, substituted aromatic groups or alkoxycarbonyl or aryloxycarbonyl (-COOR<sup>8</sup>), carboxyl (-COOH), acyloxy (-O<sub>2</sub>R<sup>8</sup>), carbamoyl (-CONR<sup>8</sup>), alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, arylalkylcarbonyl, hydroxyl (-OH), amino (NR<sup>8</sup>), halogen, allyl, alkoxy (-OR<sup>8</sup>), S-alkyl or S-aryl groups, R<sup>8</sup> representing a C<sub>1</sub> to C<sub>10</sub> alkyl or aryl group.

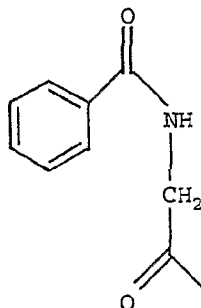
The compound of the present invention comprising a tropane derivative may be used, for example, in the diagnosis of Parkinson's disease.

One example of a compound according to the present invention may consist of a structure of formula (F) in which  $R^1$ ,  $R^3$  and  $R^4 = H$  and  $R^2$  is  $NR^5R^6$ , in which  $R^5 = H$  and  $R^6$  is chosen from:



5

The compounds in which  $R_6 =$



may be used, for example, for the diagnostic study of renal function or the therapy of renal pathologies.

10 The present invention also provides a chelation product consisting of a chelation compound according to the present invention, and of a metal or a metal complex. Examples of metals and metal complexes have been described above.

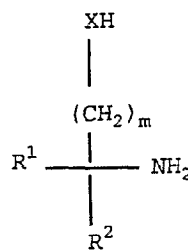
15 For example, the metal may be chosen from copper, a copper isotope and a transition metal. This may be useful, for example, as a radiopharmaceutical for therapy or diagnosis.

For example, the metal complex may be  $TcN$  or  $ReN$ .  
20 This product may then be used as a radiopharmaceutical.

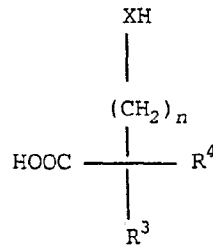
The present invention also relates to the use of a chelation compound or a chelation product according to the present invention for manufacturing a medicinal product or a diagnostic product, for example a radiopharmaceutical for therapy or diagnosis. The radiopharmaceutical may be, for example, a radiopharmaceutical for visualizing the uptake of dopamine or serotonin. Such a radiopharmaceutical may be useful for diagnosing neurodegenerative diseases, for example Parkinson's disease.

The present invention also provides a process for manufacturing a bis-dithiocarbamate compound according to the invention, comprising, successively:

- a step of protecting the XH functions of the compounds of formulae (V) and (VI) below:



(V)



(VI)

in which  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ , X, m and n are as defined in the above claim,

- a step of activating the  $-\text{COOH}$  function of compound (VI),

- a step of linking the compound of formula (V) and compound (VI) via the activated carboxyl function of compound (VI),

- a step of deprotecting the XH functions, and



- a step of reacting the deprotected XH functions with CS<sub>2</sub> to form a bis-dithiocarbamate compound according to the present invention.

One of the starting compounds comprises an acid  
5 function and the other an amine function to form the peptide bond which links these compounds. In addition, each of the compounds must comprise at least one free NH<sub>2</sub> or SH function to attach the CS<sub>2</sub>.

The aim of the step for protecting the XH  
10 functions of compounds (V) and (VI) is to protect these functions against the reagents used to activate the -COOH function of compound (VI), and to link compound (V) with the activated compound (VI). It is performed by means of conventional reagents known to those  
15 skilled in the art for protecting functions X, with X=S or NH. Examples are given below.

The other steps may each also be performed by processes known to those skilled in the art. Examples are given below to illustrate the present invention.

20 The base of the chelation compound of the present invention may be, for example, a combination of two natural or unnatural amino acids containing two amine functions in ε-terminal positions and, on axial chains, a function which will serve to functionalize the vector  
25 molecule for use in radiopharmacy. The amine functions in ε-terminal positions are modified into dithiocarbamate functions et serve to complex the metal, also known as the metallic core.

The present invention also relates to a process  
30 for manufacturing a compound according to the present invention, the said process comprising a process for

manufacturing a bis-dithiocarbamate compound according to the invention, and also comprising a step of attaching a radical  $R^5$  and optionally  $R^6$  to this bis-dithiocarbamide structure or to an intermediate product  
5 in its manufacture to obtain a chelation compound according to the invention as defined above.

The present invention thus provides a family of complexing agents which attach a metal, for example a radioelement, on the one hand, and which, by virtue of  
10 their functionalization, may be linked to a vector molecule either via a final synthesis (linking of radicals  $R^5$  or  $R^6$ ), or during the synthesis of a vector molecule or a peptide.

The compound for chelating a metal or a metal  
15 complex of the present invention may, for example, on the one hand, attach a radioelement, and, on the other hand, be linked to a vector molecule either via a final synthesis, or during the synthesis of a vector molecule or a peptide.

20 The present invention also relates to a process for manufacturing a compound according to the invention, the said process comprising:

- a step of reacting two  $\epsilon$ - $NH_2$  functions of two contiguous amino acids of a precursor molecule  
25 of the compound according to Claim 1 or 2 with  $CS_2$  so as to form a compound according to Claim 1 or 2,

the precursor molecule constituting the radical  $R^5$  and optionally the radical  $R^6$ .

30 The precursor molecule may be, for example, in the form of the compounds (V) and (VI) described above

linked via a peptide bond formed between the  $\text{NH}_2$  and  $\text{COOH}$  side functions.

The compound of the present invention may thus also be obtained, for example, by dithiocarbamate (DTC) labelling of two contiguous natural or unnatural amino acids, on the  $\text{NH}_2$  functions of the side chains, or on an  $\text{NH}_2$  function of a side chain and an N-terminal  $\text{NH}_2$  function in the case of a dipeptide or of a reaction at the N-terminal end of a peptide or a protein. It may also be obtained by DTC-labelling of an organic molecule comprising a peptide bond and two amine functions separated by at least seven carbons.

The process of the present invention may be used, for example, to manufacture a chelation product according to the invention defined above, comprising the manufacture of a bis-dithiocarbamate compound according to the invention according to a manufacturing process of the present invention, and a reaction for complexing a metal or a metal complex via the said bis-dithiocarbamate compound manufactured.

The metal or the metal complex may be as defined above.

The present invention also provides a diagnostic kit comprising a chelating compound according to the present invention.

Other characteristics and advantages of the invention will also emerge on reading the examples which follow.

**EXAMPLES****A) EXAMPLES OF THE PREPARATION OF BIS-DITHIOCARBAMATES ACCORDING TO THE PRESENT INVENTION**  
**5 FROM DIPEPTIDES**

Example 1 : Preparation of bis-dithiocarbamates from the following sequences: lysine-lysines (1), alanine-lysine (2) and glycine-lysine (3)

Each diamino molecule (0.5 mmol) is suspended in  
10 10 ml of ethanol and sodium hydroxide pellets (0.08 g ; 2 mmol) are added along with the minimum amount of water required to dissolve the amino molecule. The mixture is left stirring for 1 hour and the water/ethanol mixture is then evaporated off under reduced  
15 pressure at low temperature. The oil obtained is taken up in alcohol, 3 sodium hydroxide pellets are added and an excess of pure carbon disulphide CS<sub>2</sub> is then introduced dropwise. A yellow coloration appears after half an hour, and the copper sulphate test is positive.  
20 This test was performed by placing a drop of reaction mixture on a silica plate and then, on this drop, a drop of copper sulphate in water: a brown spot is observed if the bis-dithiocarbamate is formed. After stirring for 4 hours, the solvent is evaporated off to  
25 dryness, giving a yellow paste.

HPLC analysis : C18-5 µm-25 cm-YMC column; flow rate 1 ml/minute; UV detection at 300 nm; eluents A=water; B=methanol; gradient 0 to 5 minutes 0% of B - from 5 to 20 minutes 0 to 100% of B - from 20 to  
30 25 minutes 100% of B; 25 to 25.1 minutes 100 to 0% of B - 25.1 to 30 minutes 0% of B. Purity of the

synthesized products greater than 95% in the three cases.

Example 2: Radiolabelling of the lysine-lysines  
5 (DTClys-lysDTC): compound (4); alanine-lysine (DTCala-lysDTC): compound (5) and glycine-lysine (DTCgly-lysDTC): compound (6) bis-dithiocarbamates

Protocol for radiolabelling with  $^{99}\text{Tc}$  :

10 a-intermediate solution: a lyophilisate containing hydrazine (SDH) 5 mg, 1,2-propanediamino-N,N,N',N'-tetraacetic acid (PDTA) 5 mg, 10  $\mu\text{g}$  of stannic chloride is taken up in 1 ml of injection-grade water. 1 ml of  $^{99}\text{TcO}_4^-$  is added. The mixture  
15 is left to act for 30 minutes.

b-exchange reaction: 1.8 mg of bis-dithiocarbamate dissolved in a 0.1 M pH 7.4 phosphate buffer are mixed with 0.5 ml of the preceding intermediate solution. The  
20 mixture is left to act for 2 hours.

The reactions are analysed by HPLC. The results of these analyses are given in Table I below:

Product	Detection	Number of peaks
(DTCgly-lysDTC)	radioactive	9 peaks
(DTCala-lysDTC)	radioactive	6 peaks
(DTClys-lysDTC)	radioactive	1 peak

25 The first two bis-dithiocarbamates react inter-molecularly whereas the (DTCgly-lysDTC) bis-dithiocarbamate reacts via an intramolecular reaction.

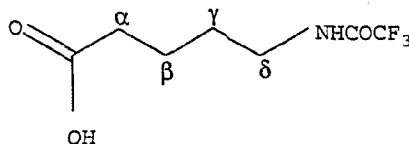
B) EXAMPLES OF STEPS FOR PROTECTING THE XH  
FUNCTIONS OF COMPOUNDS OF FORMULAE V AND VI ACCORDING  
TO THE PROCESS OF THE INVENTION

Example 3 : Synthesis of N-trifluoroacetyl-5-amino-  
5 valeric acid: compound (7)

1.6 equivalents of S-ethyl trifluorothioacetate  
(16 mmol; 2 ml) are added dropwise, using a syringe, to  
a solution of 5-aminovaleric acid (5a) (10 mmol;  
1.17 g) dissolved in a mixture of 1N NaOH (16 mmol;  
10 ml) [lacuna] in a three-necked flask fitted with a  
septum, through which is passed a flow of compressed  
air. A characteristic evolution of ethanethiol is  
observed.

The reaction medium is stirred for 24 hours at  
15 room temperature; a white precipitate forms. 1 ml of  
concentrated hydrochloric acid is then added. The  
precipitate is then filtered off on a sinter funnel and  
dried in the open air or in a desiccator.

The crude product is purified by recrystallization  
20 from 10 ml of a benzene/hexane mixture (1/1) to give  
1.60 g of N-trifluoroacetyl-5-aminovaleric acid of  
formula (7) below:



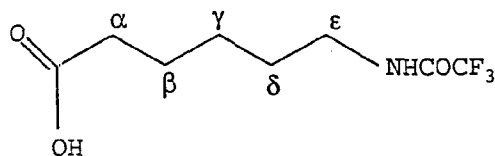
N-trifluoroacetyl-5-aminovaleric acid (compound 7)

25  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ): 1.0 (m, 4H,  $\text{H}_\beta$ ,  $\text{H}_\gamma$ ); 2.2-2.3 (m, 2H,  
 $\text{H}_\delta$ ); 3.2 (m, 2H,  $\text{H}_\alpha$ )

$^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ ): 26.5 ( $\text{C}_\beta$ ); 30; 0 ( $\text{C}_\gamma$ ); 34.1 ( $\text{C}_\alpha$ );  
39.9 ( $\text{C}_\delta$ ); 116.7 ( $\text{CF}_3$ , q,  $^1\text{J}_{\text{C-F}}=285.9$  Hz); 157.6 ( $\text{COCF}_3$ ,  
q,  $^2\text{J}_{\text{C-F}}=36.6$  Hz); 176.1 ( $\text{COOH}$ ).

Example 4: Synthesis of N-trifluoroacetyl-6-amino-  
caproic acid: compound (8)

The process is performed in the same way as in  
 5 Example 3, to give compound (8). The process is  
 commenced using 1 equivalent of 6-aminocaproic acid  
 (10 mmol; 1.31 g) dissolved in 1 equivalent of 1N NaOH  
 (10 mmol; 10 ml), to which are added 1.6 equivalents of  
 S-ethyl trifluorothioacetate (16 mmol; 2 ml). After  
 10 purification, 1.70 g of N-trifluoroacetyl-6-amino-  
 caproic acid (6b) (yield = 75%) of formula 8 below are  
 recovered:



N-trifluoroacetyl-6-aminocaproic acid (compound 8)

15  $^1\text{H NMR}$  ( $\text{D}_2\text{O}$ ): 1.13-1.37 (m, 2H,  $\text{H}_\gamma$ ); 1.45-1.54 (m,  
 4H,  $\text{H}_\beta$ ,  $\text{H}_\delta$ ); 2.21 (t, 2H,  $^3\text{J}_{\text{He-H}\delta}=7.7$  Hz,  $\text{H}_\epsilon$ ); 3.16-3.25  
 (m, 2H,  $\text{H}_\alpha$ ); 9.5 (s, 1H, NH).

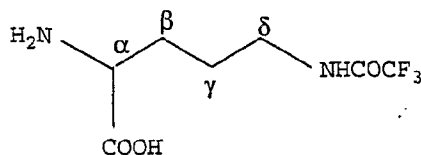
$^{13}\text{C NMR}$  (acetone): 24.8 ( $\text{C}_\beta$ ); 26.5 ( $\text{C}_\gamma$ ); 30 ( $\text{C}_\delta$ );  
 34.1 ( $\text{C}_\alpha$ ); 30.9 ( $\text{C}_\epsilon$ ); 116.7 ( $\text{CF}_3$ , q,  $^1\text{J}_{\text{C-F}}=285.9$  Hz);  
 20 157.6 ( $\text{COCF}_3$ , q,  $^2\text{J}_{\text{C-F}}=36.6$  Hz); 176.1 (COOH).

Example 5: Synthesis of N-trifluoroacetylornithine:  
compound (9)

The protocol is identical to that described above:  
 25 1.6 equivalents of  $\text{EtSCOCF}_3$  (16 mmol; 2 ml) are added  
 to a solution of ornithine monohydrochloride (10 mmol;  
 1.68 g or 1.82 g, respectively) in a mixture of 1 N  
 NaOH (10 mmol; 10 ml) [lacuna].

15

The crude product is purified by recrystallization from 10 ml of a water/ethanol mixture (1/1) to give 1.60 g of N<sup>δ</sup>-trifluoroacetylornithine of formula 9 below, in the form of a white powder, in a yield of 70%:



N<sup>δ</sup>-trifluoroacetylornithine (compound 9)

<sup>1</sup>H NMR (D<sub>2</sub>O): 1.5-2 (m, 4H, H<sub>β</sub>, H<sub>γ</sub>); 3.2-3.4 (m, 2H, H<sub>δ</sub>), 4 (t, 1H, <sup>3</sup>J<sub>Hα-Hβ</sub>=6.1 Hz).

<sup>13</sup>C NMR (D<sub>2</sub>O): 24.8 (C<sub>γ</sub>); 28.2 (C<sub>β</sub>); 39.6 (C<sub>δ</sub>); 54.8 (C<sub>α</sub>); 116.3 (CF<sub>3</sub>, q, <sup>1</sup>J<sub>C-F</sub>=285.2 Hz); 159 (C=O, q, <sup>2</sup>J<sub>C-F</sub>=35 Hz); 174.9 (COOH).

Example 6: Synthesis of N-trifluoroacetyllysine:  
compound (10)

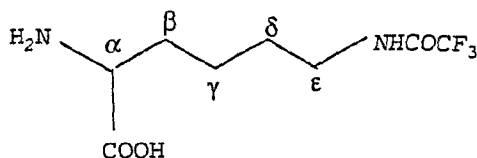
The protocol is identical to that described above: 1.6 equivalents of EtSCOCF<sub>3</sub> (16 mmol; 2 ml) are added to a solution of lysine monohydrochloride (10 mmol; 1.82 g) in a mixture of 1 N NaOH (10 mmol; 10 ml) [lacuna].

The crude product is purified by recrystallization from 10 ml of a water/ethanol mixture (1/1) to give 1.70 g of N<sup>ε</sup>-trifluoroacetyllysine of formula 10 below, in the form of a white powder, in a yield of 70%.

25



16



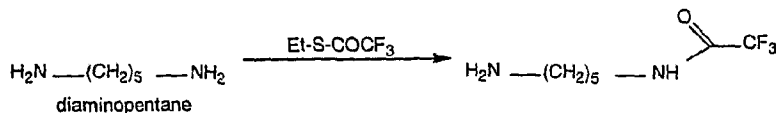
N<sup>ε</sup>-trifluoroacetyllysine  
(compound 10)

5           <sup>1</sup>H NMR (D<sub>2</sub>O): 1.2-1.3 (m, 2H, H<sub>δ</sub>); 1.4-1.6 (m, 2H, H<sub>γ</sub>), 1.7-1.8 (m, 2H, H<sub>β</sub>); 3.2 (t, 2H, <sup>3</sup>J<sub>Hε-Hδ</sub>=6.5 Hz, H<sub>ε</sub>); 3.6 (t, 1H, <sup>3</sup>J<sub>Hα-Hβ</sub>=6.2 Hz, H<sub>α</sub>).

<sup>13</sup>C NMR (D<sub>2</sub>O): 25.9 (C<sub>γ</sub>); 28.5 (C<sub>δ</sub>); 31.7 (C<sub>β</sub>); 37.3 (C<sub>ε</sub>); 46.8 (C<sub>α</sub>); 113.7 (CF<sub>3</sub>, q, <sup>1</sup>J<sub>C-F</sub>=287.8 Hz); 155.2  
10 (C=O, q, <sup>2</sup>J<sub>C-F</sub>=37.14 Hz); 167.3 (COOH).

Example 7: Synthesis of N<sup>ε</sup>-trifluoroacetyldiaminopentane: compound (22)

50 mmol of diaminopentane are dissolved in 100 ml  
15 of methanol. A solution of 50 mmol of ethyl trifluorothioacetate in 10 ml of methanol is added dropwise. The reaction mixture is stirred for 3 hours. After evaporating off the solvent, a yellow oil is obtained, which partially crystallizes in ice. This  
20 synthesis may be represented schematically in the following manner:



N<sup>ε</sup>-trifluoroacetyldiaminopentane  
(compound 22)

17

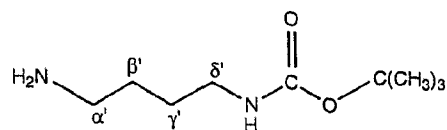
A purification is performed by flash chromatography on silica gel, with the eluent:  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (90/10).

5        **I.R. (KBr):** 3500-3400  $\text{cm}^{-1}$  (v NH amide and amine, broad band), 2867  $\text{cm}^{-1}$  (v  $\text{CH}_2$  of the alkyl chain), 1711  $\text{cm}^{-1}$  (v CO of the amide), 1490  $\text{cm}^{-1}$  (v CH of s  $\text{CH}_2$ ).

<sup>1</sup>H NMR (DMSO  $\text{D}_6$ ): 3.13 [t(J=7.05 Hz); 2H;  $\text{CH}_2\alpha$ ];  
 2.46 [t(J=6.54 Hz); 2H;  $\text{CH}_2\epsilon$ ]; 1.43 [m(J $\approx$ 7 Hz); 2H;  $\text{CH}_2\beta$ ];  
 10    1.24 [m; 4H;  $\text{CH}_2\delta$  and  $\gamma$ ].

<sup>13</sup>C NMR (DMSO): 156.1 [q;  $\text{C}=\text{O}$  of the trifluoroacetamide]; 116 [q;  $\text{CF}_3$ ]; 41.5, 39.2, 32.8, 28.2, 23.6 [s, 5  $\text{CH}_2$ ].

15    Example 8: Synthesis of N $^{\alpha}$ -Boc-diaminobutane: compound (27)



compound (27)

20        A solution of di-tert-butyl dicarbonate (4.9 g, 0.022 mol) in dioxane (60 ml) is added over a period of 2.5 hours to a solution of 1,4-butanediamine (15.51 g, 0.176 mol) in dioxane (60 ml). The mixture is stirred for 22 hours and the solvent is evaporated off on a  
 25    rotavapour. Water (50 ml) is added to the residue and the insoluble disubstituted product is recovered by filtration. The filtrate is dried with anhydrous magnesium sulphate. Next, it is extracted with

methylene chloride (3 x 50 ml). After evaporating off the solvent, 3.4 g of a colourless oil (compound 27) (81%) are obtained, and gradually solidified to give a white solid (m.p. = 112°C, Lit\*.m.p. = 110-112°C).

5

\*A.P. Krapcho, C.S. Kuell, Mono-protected diamines, N-tert-butoxycarbonyl- $\alpha$ - $\omega$ -alkanediamines From  $\alpha$ , $\omega$ -Alkanediamines, Synthetic Communications, 1990, 20, 2559-2564.

10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ (ppm)=1.28 (s, 2H,  $\text{NH}_2$ ); 1.3-1.6 (m, 4H,  $\text{H}_\gamma$ ,  $\text{H}_\beta$ ); 1.45 (s, 9H); 2.65 (t, 2H,  $\text{H}_\alpha$ ); 3.04 (q, 2H,  $\text{H}_\delta$ ); 4.7 (sl, 1H).

$^{13}\text{C}$  NMR (50.2 MHz,  $\text{CDCl}_3/\text{CHCl}_3$ : 77 ppm/TMS):  $\delta$  (ppm)=155.80 ( $\text{COOC}(\text{CH}_3)_3$ ); 78.72 ( $\text{C}(\text{CH}_3)_3$ ); 41.57 ( $\text{C}_\delta$ );  
15 40.16 ( $\text{C}_\alpha$ ); 30.62 ( $\text{C}_\gamma$ ); 28.16 ( $(\text{CH}_3)_3$ ); 27.24 ( $\text{C}_\beta$ ).

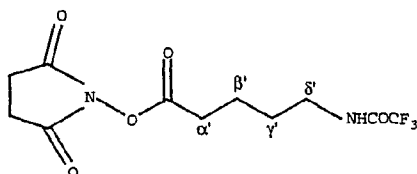
**C) EXAMPLES OF STEPS FOR ACTIVATING THE COOH FUNCTIONS OF THE COMPOUNDS OF FORMULA VI ACCORDING TO THE PROCESS OF THE INVENTION**

20 Example 9: Activation of the acid functions of compounds (7) and (8)

470 mg of compound (7). - or 500 mg of compound (8) - (2.20 mmol) are dissolved in 20 ml of ethyl acetate in a 50 ml round-bottomed flask. 1 equivalent of N-hydroxysuccinimide (2.20 mmol; 253 mg) is added.  
25 1 equivalent of dicyclohexylcarbodiimide (2.20 mmol, 454 mg) is added to this clear solution. The mixture is stirred for 24 hours at room temperature. A white precipitate of N,N'-dihexylurea appears rapidly, and is  
30 removed by filtration through a sinter funnel. The

filtrate is recovered and evaporated. A pale yellow oil is obtained, which is taken up, if necessary, in a small amount of ethyl acetate, and the mixture is refiltered. This operation removes the remaining urea.

- 5 The filtrate is evaporated to give a transparent oil which crystallizes at room temperature to give 682 mg of compound (11) - or 713 mg of compound (12) - in the form of a pearlescent white solid (yield = 90%).

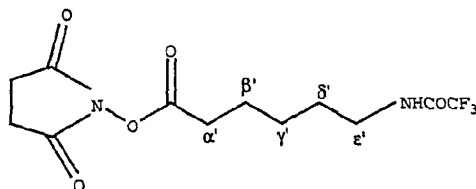


- 10 N'-succinimidyl N-trifluoroacetyl-5-aminovalerate  
(compound 11)

- <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 1.25-1.9 (m, 4H, H<sub>β</sub>, H<sub>γ</sub>); 2.6 (t, 2H, <sup>3</sup>J<sub>Hδ'-HY'</sub>=6.3 Hz); 2.8 (s, 4H, H<sub>succinimide</sub>); 3.2-3.4 (m, 15 2H, H<sub>α'</sub>); 7.4 (s, 1H, NH).

<sup>13</sup>C NMR (CDCl<sub>3</sub>): 22.0 (C<sub>β'</sub>); 30.7 (C<sub>γ'</sub>); 39.5 (C<sub>δ'</sub>); 60.8 (C<sub>α'</sub>); 119.1 (CF<sub>3</sub>, q, <sup>1</sup>J<sub>C-F</sub>=287.6 Hz); 157.5 (COCF<sub>3</sub>, q, <sup>2</sup>J<sub>C-F</sub>=36.78 Hz); 168.7 and 169.9 (2 CO<sub>succinimide</sub>); 171.8 (CO-O).

20



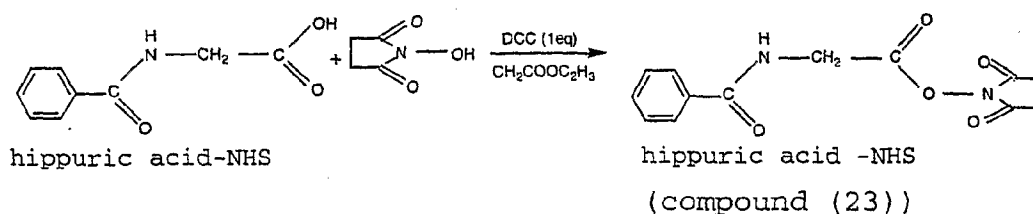
N'-succinimidyl N-trifluoroacetyl-6-aminocaproate  
(compound 12)

5

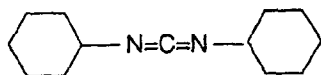
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 1.2-2.0 (m, 6H,  $\text{H}_\beta$ ,  $\text{H}_\gamma$ ,  $\text{H}_\delta$ ); 2.5 (t, 2H,  $^3\text{J}_{\text{H}\delta-\text{H}\epsilon}=6.5$  Hz); 2.8 (s, 4H,  $\text{H}_{\text{succinimide}}$ ); 3.2-3.3 (m, 2H,  $\text{H}_\alpha$ ); 7.5 (s, 1H, NH).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 21.4 ( $\text{C}_\gamma$ ); 22.0 ( $\text{C}_\beta$ ); 28.0 ( $\text{C}_\delta$ );  
10 39.6 ( $\text{C}_\epsilon$ ); 60.8 ( $\text{C}_\alpha$ ); 119.0 ( $\text{CF}_3$ , q,  $^1\text{J}_{\text{C-F}}=289.3$  Hz);  
157.5 ( $\text{COCF}_3$ , q,  $^2\text{J}_{\text{C-F}}=36.7$  Hz); 168.6 and 168.8 (2  
CO<sub>succinimide</sub>); 171.7 (CO-O).

Example 10: Activation of hippuric acid with N-hydroxy-  
15 succinimide: compound (23)



20



DCC dicyclohexylcarbodiimide

17.3 mmol (2 g) of N-hydroxysuccinimide are  
dissolved in 60 ml of ethyl acetate. 17.3 mmol (3.1 g)  
25 of hippuric acid are added. A solution of 17.3 mmol

(3.57 g) of dicyclohexylcarbodiimide in 15 ml of ethyl acetate is then added. A voluminous white precipitate forms. The reaction mixture is stirred for 15 hours. The solution is filtered and a white solid is recovered.

**Purification:**

Cold fractional recrystallization from ethyl acetate.

m.p. = 149-150°C.

10

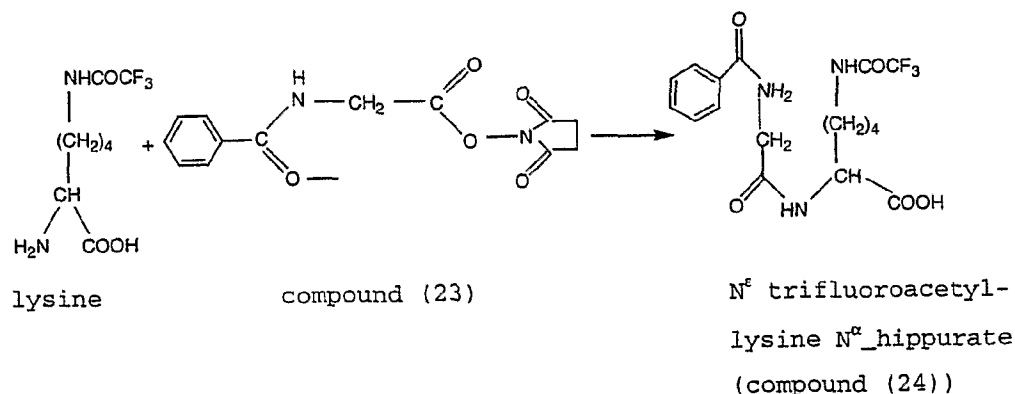
**I.R. (KBr):** 3357  $\text{cm}^{-1}$  (strong band;  $\nu$  N-H of the amide), 1813, 1785, 1740  $\text{cm}^{-1}$  ( $\nu$  C=O of the 4 carbonyl functions) 1640, 1579  $\text{cm}^{-1}$  ( $\nu$  of the aromatic rings).

**$^1\text{H}$  NMR (DMSO  $\text{D}_6$ ):** 9.2 [t; 1H; NH amide]; 7.9 [d; 2H; aromatic  $\text{H}_{\text{ortho}}$ ]; 7.5 [m; 3H;  $\text{H}_{\text{meta}}$  and  $\text{H}_{\text{para}}$ ]; 4.45 [d; 2H; aliphatic  $\text{CH}_2$ ]; 2.8 [s; 4H; 2 cyclic  $\text{CH}_2$ ].

15

Example 11 a): Coupling of hippuric acid and lysine to form compound (24)

20



25

1.5 mmol (0.5 g) of compound 23 are dissolved in 20 ml of tetrahydrofuran. 1.5 mmol (0.4 g) of  $\text{N}^\epsilon$ -tri-

fluoroacetyllysine and 1.5 mmol (0.2 ml) of triethylamine are then added and, after stirring for 20 hours, the mixture is clear. The THF is evaporated off and the oil obtained is taken up in ethyl acetate and washed with water. The aqueous phase is acidified with a few drops of concentrated acetic acid and then extracted with dichloromethane. A white solid precipitates in the organic phase (product).

<sup>1</sup>H NMR (DMSO D<sub>6</sub>): 9.4 [t; 1H, NH of the hippuric acid]; 8.7 [t; 1H; NH trifluoroacetamide]; 8.2 [d; 1H; amide NH of the coupling]; 7.8 [d; 2H, H<sub>ortho</sub>]; 7.5 [m; 3H; H<sub>para</sub> and 2 H<sub>meta</sub>]; 3.9 [t; 2H; CH<sub>2</sub> of the hippuric acid]; 3.1 [m; 2H; CH<sub>2</sub>ε]; 1.1-1.8 [3 m; 6H; 3 CH<sub>2</sub> of the aliphatic chain].

Example 11 b): Activation of N<sup>ε</sup>-trifluoroacetyllysine N<sup>α</sup>-hippurate: (compound 24) with N-hydroxysuccinimide to form compound (25)

10 mmol (2 g) of N-hydroxysuccinimide are dissolved in 60 ml of ethyl acetate. 10 mmol of N<sup>ε</sup>-trifluoroacetyllysine N<sup>α</sup>-hippurate are added. A solution of 10 mmol of dicyclohexylcarbodiimide in 20 ml of ethyl acetate is added. The reaction mixture is stirred for 24 hours. The solution is filtered and a white solid is recovered.

<sup>1</sup>H NMR (DMSO D<sub>6</sub>): 9.4 [t; 1H, NH of the hippuric acid]; 8.7 [t; 1H; NH trifluoroacetamide]; 8.2 [d; 1H; amide NH of the coupling]; 7.8 [d; 2H, H<sub>ortho</sub>]; 7.5 [m;

3H;  $H_{\text{para}}$  and 2  $H_{\text{meta}}$ ]; 3.9 [t; 2H;  $\text{CH}_2$  of the hippuric acid]; 3.1 [m; 2H;  $\text{CH}_2\epsilon$ ]; 2.8 [s; 4H; 2  $\text{CH}_2$ ]; 1.1-1.8 [3 m; 6H; 3  $\text{CH}_2$  of the aliphatic chain].

5 **Purification:**

Cold fractional recrystallization from ethyl acetate.

10 **D) EXAMPLES OF STEPS FOR LINKING A COMPOUND OF FORMULA V AND A COMPOUND OF FORMULA VI ACTIVATED VIA ITS CARBOXYL FUNCTION ACCORDING TO THE PROCESS OF THE INVENTION**

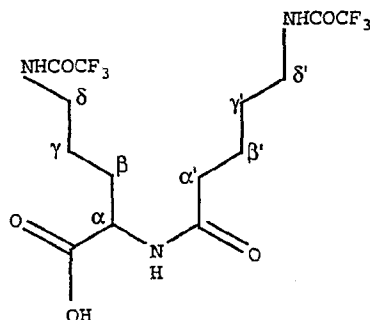
Example 12: Synthesis of  $\text{N}^\delta, \text{N}^\delta$ -bis(trifluoroacetyl)-N-(5-aminopentanoyl)ornithine: compound (13)

15 1 equivalent of compound (9) or [lacuna] (2 mmol; i.e. 456 mg) is dissolved in 10 ml of dimethylformamide in a 25 ml round-bottomed flask. A suspension is obtained, to which is added 1 ml of triethylamine and 1.5 equivalents of compound (11) (3 mmol; 639 mg or  
20 681 mg, respectively). The reaction mixture is stirred for 24 hours at room temperature to give a clear solution.

The mixture is then made alkaline by successive additions of a sodium carbonate solution until a pH = 8  
25 is obtained. Next, the mixture is extracted with twice 15 ml of ethyl acetate. The aqueous phase is recovered and hydrolysed with a few ml of concentrated hydrochloric acid until a pH = 2 is obtained. The resulting mixture is extracted with three times 15 ml  
30 of ethyl acetate. The organic phases are then washed with water to remove the remaining DMF, and then with



brine and are dried over  $\text{Na}_2\text{SO}_4$ . The solvent is then evaporated off to give a clear oil which crystallizes at room temperature. The yield is 70%.



- 5  $\text{N}^\delta, \text{N}$ -bis(trifluoroacetyl)- $\text{N}$ -(5-aminopentanoyl)ornithine  
(compound 13)

$^1\text{H}$  NMR (acetone): 1.5-2.2 (2m, 8H,  $\text{H}_\beta\text{H}_{\beta'}$ ,  $\text{H}_\gamma, \text{H}_{\gamma'}$ );  
2.3 (m, 2H,  $\text{H}_\alpha$ ); 3.4 (t, 4H,  $\text{H}_\delta\text{H}_{\delta'}$ ,  $^3\text{J}_{\text{H}\delta-\text{H}\gamma}=6$  Hz,  
 $^3\text{J}_{\text{H}\delta'-\text{H}\gamma'}=6$  Hz); 4.5 (m, 1H,  $\text{H}_\alpha$ ); 7.6 (d, 1H,  
10  $^3\text{J}_{\text{NH}-\text{H}\alpha}=7.6$  Hz); 8.6 (s 2H, 2 $\text{NHCOCF}_3$ ).

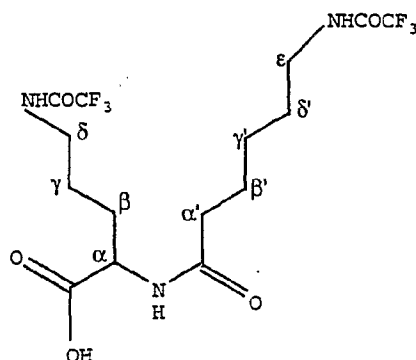
$^{13}\text{C}$  NMR (DMSO  $d_6$ ): 23.3 to 29.2 ( $\text{C}_\beta\text{C}_{\beta'}, \text{C}_\gamma\text{C}_{\gamma'}$ ); 36.6  
( $\text{C}_\alpha$ ); 41.1 and 41.9 ( $\text{C}_\delta\text{C}_{\delta'}$ ); 52.3 ( $\text{C}_\alpha$ ); 116.8 ( $\text{CF}_3$ , q,  
 $^1\text{J}_{\text{C}-\text{F}}=288.3$  Hz); 157.0 ( $\text{COCF}_3$ , q,  $^2\text{J}_{\text{C}-\text{F}}=36.7$  Hz); 172.9  
(CONH); 174.5 (COOH).

15

Example 13: Synthesis of  $\text{N}^\delta, \text{N}$ -bis(trifluoroacetyl)- $\text{N}$ -(5-aminohexanoyl)ornithine: compound (14)

The process is performed in the same manner as in  
Example 12 with 1 equivalent of compound (9) (2 mmol;  
20 i.e. 456 mg). Compound (11) is replaced with  
1.5 equivalents of compound (12) (3 mmol; i.e. 681 mg).  
The yield is 70%.

25



$N^{\delta},N^{\epsilon'}$ -bis(trifluoroacetyl)-N-(6-aminohexanoyl)ornithine  
(compound 14)

5  $^1\text{H}$  NMR (DMSO  $d_6$ ): 1.1-1.8 (m, 10H,  $H_{\beta}H_{\beta'}$ ,  $H_{\gamma}H_{\gamma'}$ ,  $H_{\delta}$ );  
2.1 (t, 2H,  $^3J_{H_{\alpha'}-H_{\beta'}}=7.2$  Hz,  $H_{\alpha'}$ ); 3.2 (m, 4H,  $H_{\epsilon}$ ,  $H_{\delta}$ ); 4.1  
(m, 1H,  $H_{\alpha}$ ); 8.1 (d, 1H,  $^3J_{\text{NH}-H_{\alpha}}=7.7$  Hz, NH); 9.4 (s, 2H,  
2NHCOCF<sub>3</sub>).

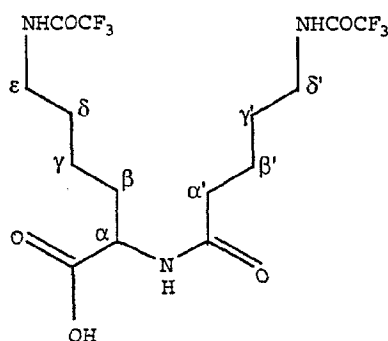
10  $^{13}\text{C}$  NMR (DMSO  $d_6$ ): 27.4 to 30.9 ( $C_{\beta}C_{\beta'}$ ,  $C_{\gamma}C_{\gamma'}$ ,  $C_{\delta}$ ); 37  
( $C_{\alpha'}$ ); 41 ( $C_{\epsilon}$ ,  $C_{\delta}$ ); 54 ( $C_{\alpha}$ ); 120 (2 CF<sub>3</sub>,  $^1J_{\text{C-F}}=288.2$  Hz);  
158.6 (2 C=O, q,  $^2J_{\text{C-F}}=39.0$  Hz); 174.9 (CONH); 176.2  
(COOH).

15 Example 14: Synthesis of  $N^{\delta},N^{\epsilon'}$ -bis(trifluoroacetyl)-N-(5-aminopentanoyl)lysine: compound (15)

1 equivalent of compound (10) (2 mmol; i.e. 484 mg) is dissolved in 10 ml of dimethylformamide in a 25 ml round-bottomed flask. A suspension is obtained, to which is added 1 ml of triethylamine and  
20 1.5 equivalents of compound (11) (3 mmol; i.e. 639 mg or 681 mg). The reaction mixture is stirred for 24 hours at room temperature to give a clear solution.

The mixture is then made alkaline by successive additions of a sodium carbonate solution until a pH = 8

is obtained. Next, the mixture is extracted with twice 15 ml of ethyl acetate. The aqueous phase is recovered and hydrolysed with a few ml of concentrated hydrochloric acid until a pH = 2 is obtained. The  
 5 resulting mixture is extracted with three times 15 ml of ethyl acetate. The organic phases are then washed with water to remove the remaining DMF, and then with brine and are dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent is then evaporated off to give a clear oil which crystallizes  
 10 at room temperature. The yield is 70%.



N<sup>ε</sup>,N<sup>δ'</sup>-bis(trifluoroacetyl)-N-(5-aminopentanoyl)lysine  
 (compound 15)

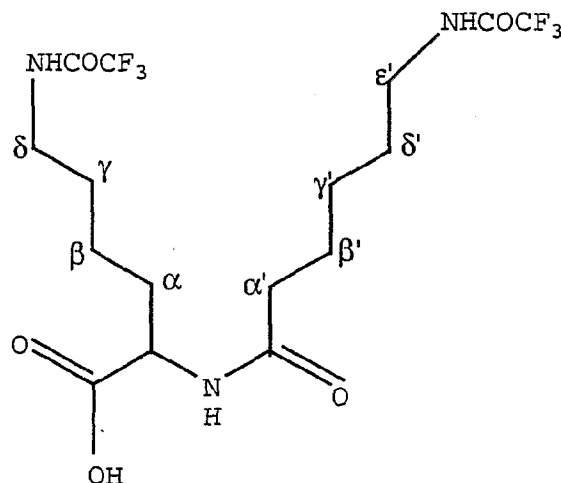
15

<sup>1</sup>H NMR (200 MHz, acetone): 1.1-1.8 (m, 5H, H<sub>β</sub>H<sub>β'</sub>, H<sub>γ</sub>H<sub>γ'</sub>); 2.2 (t, 2H, <sup>3</sup>J<sub>Hα'-Hβ</sub>=6.5 Hz, H<sub>α'</sub>); 3.2 (m, 4H, H<sub>ε</sub>H<sub>δ</sub>); 4.3 (m, 1H, H<sub>α</sub>); 7.5 (d, 1H, <sup>3</sup>J<sub>NH-Hα</sub>=7.8 Hz, NH); 8.4 (s, 2H, 2NHCOCF<sub>3</sub>).

20 <sup>13</sup>C NMR (acetone): 23 to 31 (C<sub>β</sub>C<sub>β'</sub>, C<sub>γ</sub>C<sub>γ'</sub> and C<sub>δ</sub>); 39 (C<sub>α'</sub>); 49 (C<sub>ε</sub>C<sub>δ</sub>); 52 (C<sub>α</sub>); 117 (2 CF<sub>3</sub>, <sup>1</sup>J<sub>C-F</sub>=287.4 Hz); 156 (2 C=O, <sup>2</sup>J<sub>C-F</sub>=35.3 Hz); 173.5 (CONH); 173.7 (COOH).

Example 15: Synthesis of  $N^{\delta}, N^{\delta'}$ -bis(trifluoroacetyl)-N-(5-aminohexanoyl)lysine: compound (16)

The process is performed in the same manner as in Example 14, with 1 equivalent of compound (10) (2 mmol; i.e. 456 mg or 484 mg). Compound (11) is replaced with 1.5 equivalents of compound (12) obtained in Example 9 above (3 mmol; i.e. 681 mg). The yield is 70%.



$N^{\delta}, N^{\delta'}$ -bis(trifluoroacetyl)-N-(6-aminohexanoyl)lysine  
(compound 16)

10

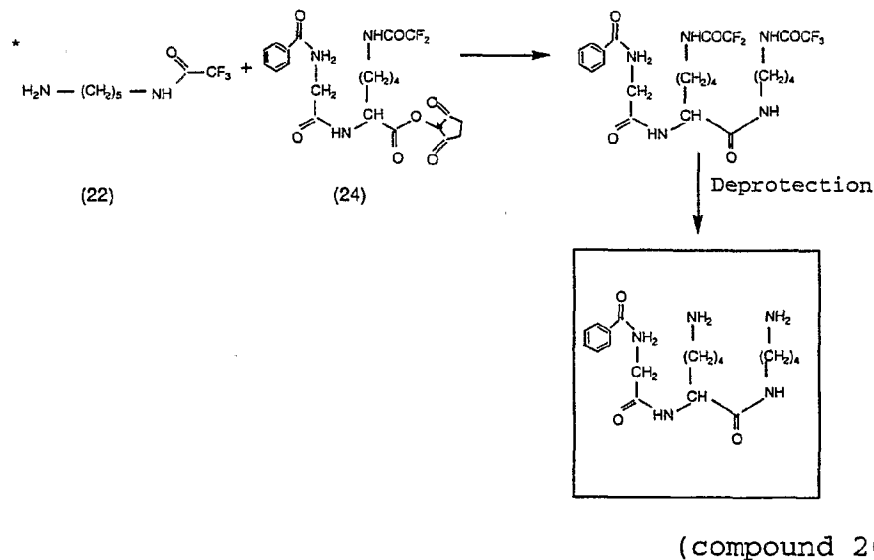
$^1\text{H}$  NMR (DMSO  $d_6$ ): 1.2-1.7 (3m, 12H,  $H_{\beta}H_{\beta'}, H_{\gamma}H_{\gamma'}, H_{\delta}H_{\delta'}$ );  
2.1 (t, 2H,  $^3J_{H_{\alpha'}, H_{\beta}}=7.3$  Hz,  $H_{\alpha'}$ ); 3.1-3.25 (m, 4H,  
 $H_{\epsilon}, H_{\epsilon'}$ ); 4.0-4.2 (m, 1H,  $H_{\alpha}$ ); 8.1 (d, 1H,  $^3J_{NH-H_{\alpha}}=7.7$  Hz,  
15 NH); 9.5 (s, 2H, 2NHCOCF<sub>3</sub>); 12.3 (s, 1H, COOH).

$^{13}\text{C}$  NMR (DMSO  $d_6$ ): 23.5-34.3 ( $C_{\beta}C_{\beta'}, C_{\gamma}C_{\gamma'}, C_{\delta}C_{\delta'}$ ); 36.6  
( $C_{\alpha'}$ ); 116.8 (2 CF<sub>3</sub>, q,  $^1J_{C-F}=287.8$  Hz); 156.8 (2  $\text{COCF}_3$ ,  
q,  $^2J_{C-F}=35.7$  Hz); 173.1 (CONH); 174.6 (COOH).

Example 17: Coupling of N<sup>ε</sup>-trifluoroacetyllysine N<sup>α</sup>-hippurate NHS (24) to N<sup>ε</sup>-trifluoroacetyldiaminopentane (22) to form compound (26)

1.5 mmol of N<sup>ε</sup>-trifluoroacetyllysine N<sup>α</sup>-hippurate NHS (24) are dissolved in 50 ml of tetrahydrofuran. 1.5 mmol of N<sup>ε</sup>-trifluoroacetyldiaminopentane (22) and 1.5 mmol (0.2 ml) of triethylamine are then added and, after stirring for 20 hours, the mixture is clear. The THF is evaporated off and the oil obtained is taken up in ethyl acetate and washed with water. The aqueous phase is acidified with a few drops of concentrated acetic acid and then extracted with dichloromethane. A white solid precipitates in the organic phase.

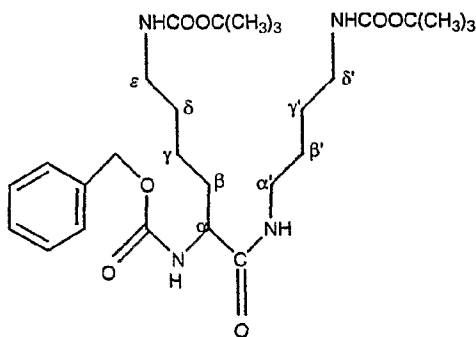
This reaction may be represented schematically in the following manner:



<sup>1</sup>H NMR (DMSO D<sub>6</sub>): 9.4 [t; 1H, NH of the hippuric acid]; 8.7 [t; 1H; NH trifluoroacetamide]; 8.2 [d; 1H; amide NH of the coupling]; 7.8 [d; 2H, H<sub>ortho</sub>]; 7.5 [m;

3H;  $H_{\text{para}}$  and 2  $H_{\text{meta}}$ ]; 3.9 [t; 2H;  $\text{CH}_2$  of the hippuric acid]; 3.1-3.2 [m; 4H]; 2.4-2.5 [t; 2]; 1.1-1.8 [m; 12H; 6  $\text{CH}_2$  of the aliphatic chains].

- 5 Example 18: Synthesis of  $\text{N}^\epsilon, \text{N}^{\delta'}$ -bis(tert-butoxycarbonyl)-( $\alpha', \delta'$ -diaminobutyl)- $\text{N}^\alpha$ (carboxybenzyloxy)-D-lysine: compound (28)



(compound 28)

0.200 g ( $1.067 \times 10^{-3}$  mol) of N-tert-butoxycarbonyl-1,4-diaminobutane (compound (27)), 0.405 g ( $1.067 \times 10^{-3}$  mol) of  $\text{N}^\alpha$ -CBz- $\text{N}^\epsilon$ -tBoc-D-lysine, 0.220 g ( $1.067 \times 10^{-3}$  mol) of 1,3-dicyclohexylcarbodiimide and 0.144 g ( $1.067 \times 10^{-3}$  mol) of 1H-hydroxybenzotriazole are dissolved in 30 ml of dry dichloromethane in a 50 ml round-bottomed flask. A white precipitate of N,N'-dicyclohexylurea appears during the reaction. The reaction mixture is stirred for 20 hours at room temperature. The filtrate is evaporated to give a white solid, which is dissolved in  $\text{H}_2\text{O}$  (20 ml) and treated with a saturated  $\text{NaHCO}_3$  solution (20 ml). The aqueous phase is extracted with dichloromethane (40 ml) and

washed with water (10 ml). The organic phase is dried over  $\text{MgSO}_4$  and evaporated to give a solid compound. The product is purified by flash chromatography (using various eluents:  $\text{CH}_2\text{Cl}_2$  alone (100 ml) followed by EtOAc (200 ml). The pure fractions lead to 0.302 g, 52%, of solid product (compound (28)), m.p. = 60-62°C.

\*  $^1\text{H}$  NMR (200.13 MHz,  $\text{CDCl}_3/\text{CHCl}_3$ ): 7.24 ppm/TMS):  
 $\delta(\text{ppm})=7.3$  (m, 5H, Ph-H); 6.4 (s, 1H,  $\text{NHCOO}$ ); 5.5 (sl, 1H,  $\text{NHCO}$ ); 5.07 (m, 1H, Ph- $\text{CH}_2\text{O}$ ); 4.07 (m, 1H,  $\text{H}_\alpha$ ); 3.24 (m, 1H,  $\text{H}_\alpha'$ ); 3.06 (m,  $\text{H}_\epsilon$ ,  $\text{H}_\delta$ ); 1.40 (m, 9H,  $(\text{CH}_3)_3$ ); 1.87-1.23 (m, 5H,  $\text{H}_\beta$ ,  $\text{H}_\beta'$ ,  $\text{H}_\delta$ ,  $\text{H}_\gamma$ ,  $\text{H}_\gamma'$ ).

\*  $^{13}\text{C}$  NMR (50.2 MHz,  $\text{CDCl}_3/\text{CHCl}_3$ : 77 ppm/TMS):  
 $\delta(\text{ppm})=171.57$  ( $\text{NHCO}$ ); 156.09 & 155.99 ( $2\times\text{COOC}(\text{CH}_3)_3$ ); 136.01 (aromatic  $\text{C}$ ); 128.32 (aromatic  $\text{CH}_2$ ); 128.00 (aromatic  $\text{CH}$ ); 127.90 (aromatic  $\text{CH}_2$ ); 79.13 ( $2\times\text{C}(\text{CH}_3)_3$ ); 66.81 (Ph- $\text{CH}_2$ ); 54.72 ( $\text{C}_\alpha$ ); 39.94 ( $\text{C}_\delta$ ); 39.75 ( $\text{C}_\epsilon$ ); 31.90 ( $\text{C}_\delta$ ); 29.41 ( $\text{C}_\gamma$ ); 28.19 ( $(\text{CH}_3)_3$ ); 27.36 ( $\text{C}_\gamma$ ); 26,15 ( $\text{C}_\beta$ ); 22.26 ( $\text{C}_\beta$ ).

\* Infrared

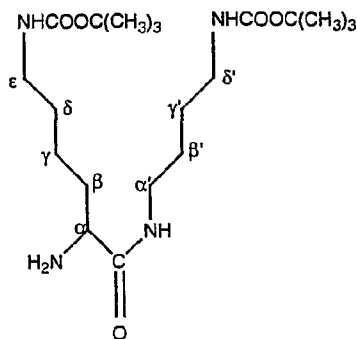
1689  $\text{cm}^{-1}$  :  $\nu(\text{NHCOO})$ ; 1652  $\text{cm}^{-1}$  :  $\nu(\text{NHCO})$ .

\* Mass spectrum

The molar mass is 550.

The peak 573 corresponds to  $(\text{M}'+\text{Na})$ .

Synthesis of  $N^{\epsilon}, N^{\delta'}$ -bis(tert-butoxycarbonyl)-( $\alpha', \delta'$ -diaminobutyl)-D-lysine: compound (29)



5

(compound 29)

0.300 g ( $5.49 \times 10^{-4}$  mol) of  $N^{\epsilon}, N^{\delta'}$ -bis(tert-butoxycarbonyl)-( $\alpha', \delta'$ -diaminobutyl)- $N^{\alpha}$ (carboxybenzyloxy)-D-lysine (compound (28)) is dissolved in 20 ml of methanol in a 50 ml round-bottomed flask, and 40 mg of Pd/C (10%) are added. The reaction mixture is stirred for 60 hours; the Pd is removed by filtration using Celite. The solvent is removed under vacuum to give a colourless liquid. This liquid, washed with hexane and dried, gives 0.205 g (90%) of compound (29) (liquid).

\*  $^1\text{H}$  NMR (200.13 MHz,  $\text{CDCl}_3/\text{CHCl}_3$ : 7.24 ppm/TMS):  
 $\delta(\text{ppm}) = 4.76$  (m, 1H,  $\text{H}_{\alpha}$ ); 3.18 (m, 1H,  $\text{H}_{\alpha}$ ); 3.04 (m, 4H,  $\text{H}_{\epsilon}$ ,  $\text{H}_{\delta'}$ ); 1.37 (m, 9H,  $(\text{CH}_3)_3$ ); 1.68-1.37 (m, 5H,  $\text{H}_{\beta}$ ,  $\text{H}_{\beta'}$ ,  $\text{H}_{\delta}$ ,  $\text{H}_{\gamma}$ ,  $\text{H}_{\gamma'}$ ).

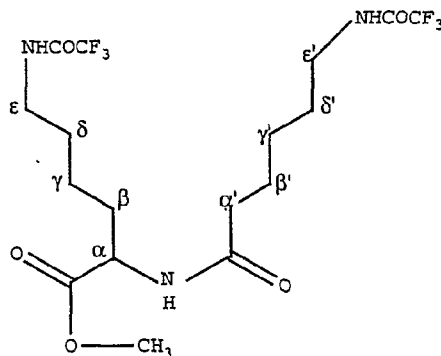
\*  $^{13}\text{C}$  NMR (50.2 MHz,  $\text{CDCl}_3/\text{CHCl}_3$ : 77 ppm/TMS):  
 $\delta(\text{ppm}) = 174.18$  ( $\text{NHCO}$ ); 155.89 ( $2 \times \text{COOC}(\text{CH}_3)_3$ ); 78.85 ( $2 \times \text{C}(\text{CH}_3)_3$ ); 54.62 ( $\text{C}_{\alpha}$ ); 39.91 ( $\text{C}_{\delta'}$ ); 38.55 ( $\text{C}_{\epsilon}$ ); 34.03



( $\underline{C}_\alpha$ ); 32.57 ( $\underline{C}_\delta$ ); 29.60 ( $\underline{C}_\gamma$ ); 28.19 ( $(\underline{CH}_3)_3$ ); 27.27 ( $\underline{C}_\gamma$ ); 26.60 ( $\underline{C}_{\beta'}$ ); 22.54 ( $\underline{C}_\beta$ ).

5 E) EXAMPLE OF A PROCESS FOR MANUFACTURING A BIS-  
DITHIOCARBAMATE COMPOUND ACCORDING TO THE PRESENT  
INVENTION IN WHICH A RADICAL R IS ATTACHED TO AN  
INTERMEDIATE PRODUCT OF THIS COMPOUND

10 Example 19: Synthesis of methyl N<sup>δ</sup>,N<sup>δ</sup>-bis(trifluoro-  
acetyl)-N-(5-aminohexanoyl)lysinate: compound (17)



methyl N<sup>ε</sup>,N<sup>ε'</sup>-bis(trifluoroacetyl)-N-(6-amino-  
hexanoyl)lysinate  
(compound 17)

100 mg (0.2 mmol) of compound (16) are dissolved in 10 ml of absolute methanol. 2 equivalents of TMCS (0.4 mmol; 56  $\mu$ l) are added slowly to this suspension and the mixture is stirred for 24 hours at room temperature. The solvent is evaporated off to give a yellow oil, which is dissolved in 20 ml of ethyl acetate. The organic phase is washed with 20 ml of a sodium carbonate solution and then with 20 ml of brine

and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent is evaporated off to give 90 mg of methyl N<sup>ε</sup>,N<sup>ε'</sup>-bis (trifluoroacetyl)-N-(6-aminohexanoyl)lysinate (compound (17)) in a yield of 90%.

5

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.25-2.0 (m, 6H, H<sub>β</sub>, H<sub>β'</sub>, H<sub>γ</sub>, H<sub>γ'</sub>, H<sub>δ</sub>, H<sub>δ'</sub>); 2.6 (m, 2H, H<sub>α'</sub>); 3.4 (m, 4H, H<sub>ε</sub>, H<sub>ε'</sub>); 3.7 (s, 3H, CH<sub>3</sub>); 4.6 (m, 1H, H<sub>α</sub>); 6.5 (d, 1H, <sup>3</sup>J<sub>NH-Hα</sub>=7.1 Hz); 7.4 (s, 2H, 2 NHCOCF<sub>3</sub>).

10 IR (cm<sup>-1</sup>): 3104, 3238, 3417, 3480 (NHCOCF<sub>3</sub> and -NH-), 1743 (C=O ester).

Example 20: Synthesis of 2β-[N<sup>δ</sup>,N<sup>δ</sup>-bis(trifluoroacetyl)-N-(5-aminopentanoyl)ornithyloxymethyl]-3β-(4'-tolyl)-tropene: compound (18)

15

0.8 equivalent of compound (13) obtained in Example 12 above (0.65 mmol, i.e. 275 mg) is added to a solution of 2β-hydroxymethyl-3β-(4'-tolyl)tropene (200 mg; 0.8 mmol) stirred at room temperature and under an inert atmosphere, for example nitrogen, in 20 ml of dichloromethane.

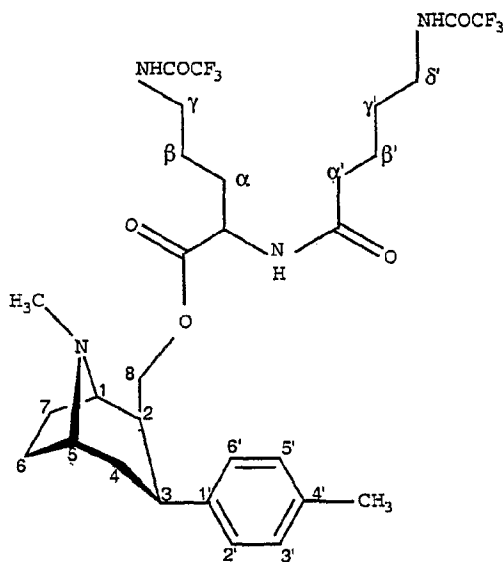
20

0.8 equivalent of DMAP (0.65 mmol; 80 mg) and 0.8 equivalent of EDCI (0.65 mmol, 125 mg) are then added. After stirring for 15 hours, the reaction medium is washed with an NaHCO<sub>3</sub> solution (20 ml) and then with 1N hydrochloric acid solution (20 ml) and finally with brine (20 ml), and the organic phases are dried over Na<sub>2</sub>SO<sub>4</sub> and then filtered. The solvent is evaporated off and a yellow oil is recovered in a yield of 50%.

25

34

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 1.3-1.5 (m, 9H,  $\text{H}_2$ ,  $\text{H}_\beta$ ,  $\text{H}_{\beta'}$ ,  $\text{H}_\gamma$ ,  $\text{H}_{\gamma'}$ );  
 1.5-1.9 (m, 3H,  $\text{H}_{4\alpha}$ ,  $\text{H}_{6\alpha}$ ,  $\text{H}_{7\alpha}$ ); 2.0-2.1 (m, 4H,  $\text{H}_{6\beta}$ ,  $\text{H}_{7\beta}$ ,  
 $\text{H}_{\alpha'}$ ); 2.2 (s, 3H,  $\text{pH-CH}_3$ ); 2.3 (s, 3H,  $\text{N-CH}_3$ ); 3.0-3.6  
 5 (m, 8H,  $\text{H}_1$ ,  $\text{H}_3$ ,  $\text{H}_5$ ,  $\text{H}_{4\beta}$ ,  $\text{H}_\delta$ ,  $\text{H}_{\delta'}$ ); 3.8-4.0 (m, 1H,  $\text{H}_\alpha$ );  
 4.3-4.5 (m, 2H,  $\text{H}_8$ ); 6.25 (m, 1H, NH); 7.1-7.2 (m, 4H,  
 aromatic H); 7.5 (m, 2H, 2  $\text{NHCOCF}_3$ ).



2 $\beta$ -[N $^\delta$ , N $^{\delta'}$ -bis(trifluoroacetyl)-N-(5-aminopentanoyl)-  
 ornithyloxymethyl]-3 $\beta$ -(4'-tolyl)tropane  
 10 (compound 18)

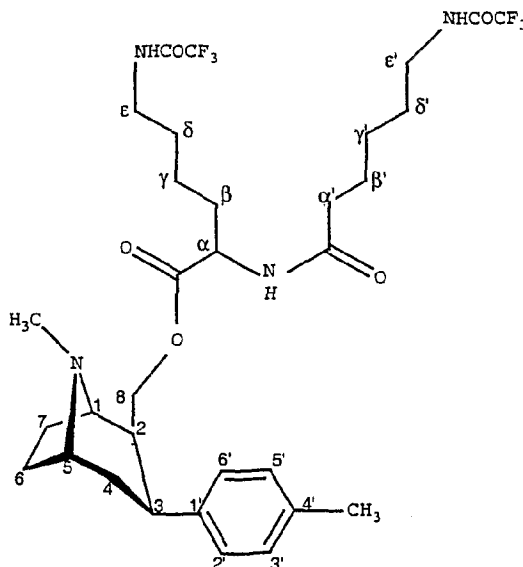
$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ): 21.2 ( $\text{Ph-CH}_3$ ); 22.6 and 25.0 ( $\text{C}_\beta$   
 and  $\text{C}_{\beta'}$ ); 25.2 ( $\text{C}_5$ ); 26.3 ( $\text{C}_7$ ); 28.5 and 28.6 ( $\text{C}_\gamma$  and  
 $\text{C}_{\gamma'}$ ); 34.2 ( $\text{C}_{\alpha'}$ ); 34.7 ( $\text{C}_3$ ); 36.2 ( $\text{C}_4$ ); 39.8 and 40.0 ( $\text{C}_\delta$   
 15 et  $\text{C}_{\delta'}$ ); 42.3 ( $\text{NCH}_3$ ); 45.7 ( $\text{C}_2$ ); 52.1 ( $\text{C}_\alpha$ ); 62.3 ( $\text{C}_5$ );  
 64.1 ( $\text{C}_8$ ); 65.6 ( $\text{C}_1$ ); 116.4 ( $\text{CF}_3$ , q,  $^1\text{J}_{\text{C-F}}=287.4$  Hz);  
 127.8 ( $\text{C}_{2'}$  and  $\text{C}_{6'}$ ); 129.4 ( $\text{C}_{3'}$ ,  $\text{C}_{5'}$ ); 136.2 ( $\text{C}_{1'}$ ); 139  
 ( $\text{C}_{4'}$ ); 157.6 (2  $\text{COCF}_3$ , q,  $^2\text{J}_{\text{C-F}}=29.3$  Hz); 172.5 ( $\text{CONH}$ );  
 173.4 and 173.6 ( $\text{CO-O}$ )- resolved signal.

20

Example 21: Synthesis of 2 $\beta$ -[N <sup>$\epsilon$</sup> ,N <sup>$\epsilon'$</sup> -bis(trifluoroacetyl)-  
N-(5-aminohexanoyl)lysinyloxymethyl]-3 $\beta$ -(4'-tolyl)-  
tropane: compound (19)

The process is performed in the same manner as in  
 5 Example 20, with a solution of 2 $\beta$ -hydroxymethyl-3 $\beta$ -(4'-  
 tolyl)tropane (200 mg; 0.8 mmol). Compound (13) is  
 replaced with 0.8 equivalent of compound (16) obtained  
 in Example 15 above, (0.65 mmol; i.e. 284 mg). The  
 solvent is evaporated off and a yellow oil is recovered  
 10 in a yield of 50%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.1-1.4 (m, 13H, H<sub>2</sub>, H <sub>$\beta$</sub> , H <sub>$\beta'$</sub> , H <sub>$\gamma$</sub> , H <sub>$\gamma'$</sub> , H <sub>$\delta$</sub> ,  
 H <sub>$\delta'$</sub> ); 1.4-1.8 (m, 3H, H<sub>4 $\alpha$</sub> , H<sub>6 $\alpha$</sub> , H<sub>7 $\alpha$</sub> ); 1.9-2.1 (m, 4H, H<sub>6 $\beta$</sub> ,  
 H<sub>7 $\beta$</sub> , H <sub>$\alpha'$</sub> ); 2.2 (s, 3H, ph-CH<sub>3</sub>); 2.3 (s, 3H, N-CH<sub>3</sub>);  
 15 3.0-3.4 (m, 8H, H<sub>1</sub>, H<sub>3</sub>, H<sub>5</sub>, H<sub>4 $\beta$</sub> , H <sub>$\epsilon$</sub> , H <sub>$\epsilon'$</sub> ); 3.6-3.85 (m,  
 2H, H<sub>8</sub>); 6.2 (m, 1H, NH); 7.1 (m, 4H, aromatic H); 7.5  
 (m, 2H, 2 NHCOCF<sub>3</sub>).



2 $\beta$ -[N <sup>$\epsilon$</sup> , N <sup>$\epsilon'$</sup> -bis(trifluoroacetyl)-N-(6-amino-  
hexanoyl)lysinyloxymethyl]-3 $\beta$ -(4'-tolyl)tropane  
(compound 19)

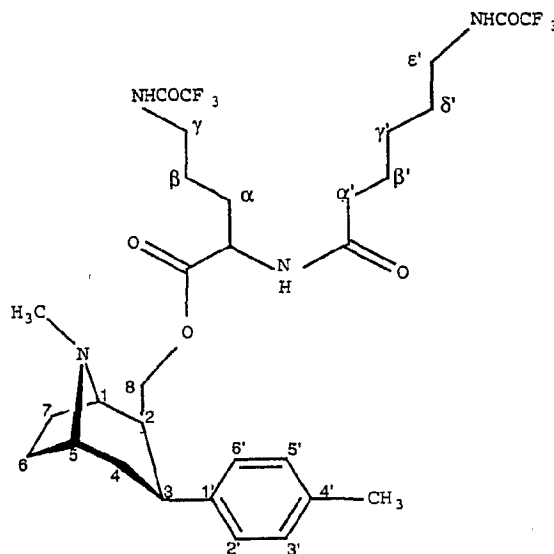
5 Example 22: Synthesis of 2 $\beta$ -[N <sup>$\delta$</sup> , N <sup>$\epsilon$</sup> -bis(trifluoroacetyl)-  
N-(5-aminohexanoyl)ornithyloxymethyl]-3 $\beta$ -(4'-tolyl)-  
tropane: compound (20)

The process is performed in the same manner as in  
Example 20, with a solution of 2 $\beta$ -hydroxymethyl-3 $\beta$ -(4'-  
10 tolyl)tropane (200 mg; 0.8 mmol). Compound (13) is  
replaced with 0.8 equivalent of compound (14) obtained  
in Example 13 above (0.65 mmol; i.e. 284 mg). The  
solvent is evaporated off and a yellow oil is recovered  
in a yield of 50%.

15

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.2-1.4 (m, 11H, H<sub>2</sub>, H $\beta$ , H $\beta'$ , H $\gamma$ , H $\gamma'$ ,  
H $\delta$ ); 1.4-1.9 (m, 3H, H<sub>4 $\alpha$</sub> , H<sub>6 $\alpha$</sub> , H<sub>7 $\alpha$</sub> ); 1.9-2.1 (m, 4H, H<sub>6 $\beta$</sub> ,  
H<sub>7 $\beta$</sub> , H $\alpha'$ ); 2.2 (s, 3H, ph-CH<sub>3</sub>); 2.3 (s, 3H, N-CH<sub>3</sub>);  
3.0-3.5 (m, 8H, H<sub>1</sub>, H<sub>3</sub>, H<sub>5</sub>, H<sub>4 $\beta$</sub> , H $\delta$ , H $\epsilon'$ ); 3.6-3.9 (m, 1H,  
20 H $\delta$ ); 4.2-4.5 (m, 2H, H $\delta$ ); 6.25 (m, 1H, NH); 7.0 (m, 4H,  
aromatic H); 7.4 (m, 2H, 2 NHCOCF<sub>3</sub>).

37



2β-[N<sup>δ</sup>,N<sup>ε'</sup>-bis(trifluoroacetyl)-N-(6-aminohexanoyl)-  
ornithyloxymethyl]-3β-(4'-tolyl)tropane  
(compound 20)

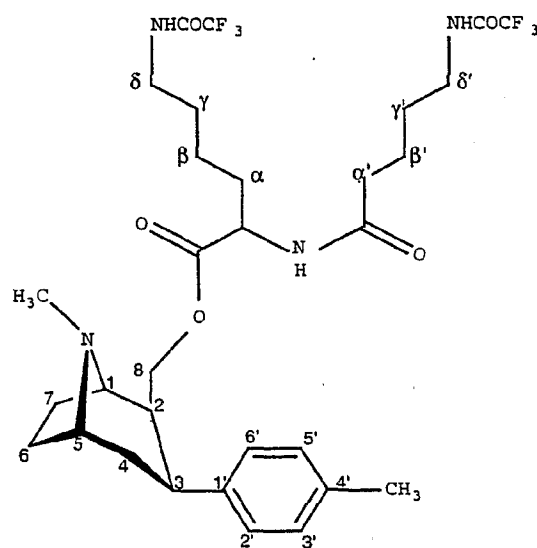
Example 23: Synthesis of 2β-[N<sup>ε</sup>,N<sup>δ</sup>-bis(trifluoroacetyl)-  
N-(5-aminopentanoyl)lysinyloxymethyl]-3β-(4'-tolyl)-  
tropane: compound (21)

10       The process is performed in the same manner as in  
Example 20 with a solution of 2β-hydroxymethyl-3β-(4'-  
tolyl)tropane (200 mg; 0.8 mmol). Compound (13) is  
replaced with 0.8 equivalent of compound (15) obtained  
in Example 14 above (0.65 mmol; i.e. 293 mg). The  
15       solvent is evaporated off and a yellow oil is recovered  
in a yield of 50%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.1-1.4 (m, 11H, H<sub>2</sub>, H<sub>β</sub>, H<sub>β'</sub>, H<sub>γ</sub>,  
H<sub>γ'</sub>); 1.4-1.8 (m, 3H, H<sub>4α</sub>, H<sub>6α</sub>, H<sub>7α</sub>); 2.0-2.1 (m, 4H, H<sub>6β</sub>,  
20       H<sub>7β</sub>, H<sub>α</sub>); 2.2 (s, 3H, ph-CH<sub>3</sub>); 2.3 (s, 3H, N-CH<sub>3</sub>);

38

2.7-3.9 (m, 1H,  $H_\alpha$ ); 4.2-4.5 (m, 2H,  $H_\beta$ ); 4.2-4.5 (m, 2H,  $H_\beta$ ); 6.2 (m, 1H, NH); 7.0 (m, 4H, aromatic H); 7.4 (m, 2H, 2  $\text{NHCOCF}_3$ ).

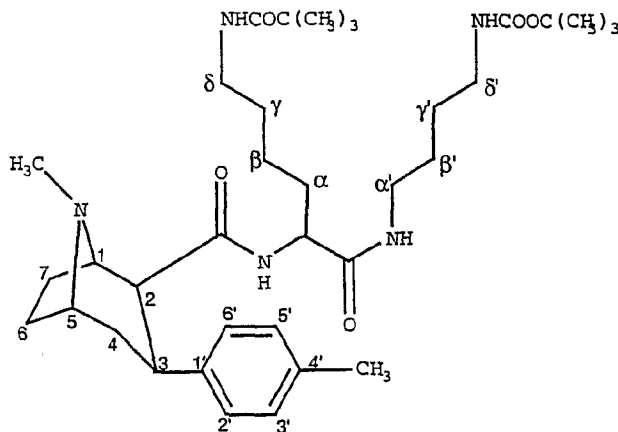


5

2 $\beta$ -[N $^\epsilon$ , N $^{\delta'}$ -bis(trifluoroacetyl)-N-(6 aminopentanoyl)-  
lysinyloxymethyl]-3 $\beta$ -(4'-tolyl)tropane  
(compound 21)

10

Example 24: 2 $\beta$ -[N <sup>$\epsilon$</sup> ,N <sup>$\delta'$</sup> -bis(tert-butoxycarbonyl)-( $\alpha'$ , $\delta'$ -diaminobutyl)-D-lysine]-3 $\beta$ -(4'-tolyl)tropane: compound (30)



(compound (30))

0.173 g ( $4.15 \times 10^{-4}$  mol), of N <sup>$\epsilon$</sup> ,N <sup>$\delta'$</sup> -bis(tert-butoxycarbonyl)-( $\alpha'$ , $\delta'$ -diaminobutyl)-D-lysine (compound 29), 0.085 g ( $4.15 \times 10^{-4}$  mol) of 1,3-dicyclohexylcarbodiimide, 0.056 g ( $4.15 \times 10^{-4}$  mol) of 1H-  
 10 hydroxybenzotriazole and 0.123 g ( $4.15 \times 10^{-4}$  mol) of 2- $\beta$ -carboxy-3 $\beta$ -tolyltropane are dissolved in 30 ml of dry dichloromethane in a 50 ml round-bottomed flask. A white precipitate of N,N'-dicyclohexylurea appears during the reaction. The reaction mixture is stirred  
 15 for 20 hours at room temperature. The filtrate, recovered and evaporated, gives a white solid which is dissolved in water H<sub>2</sub>O (10 ml) and treated with saturated NaHCO<sub>3</sub> solution (10 ml). The aqueous phase is extracted with dichloromethane (3 $\times$ 20 ml) and washed  
 20 with water (10 ml); the organic phase obtained is dried over MgSO<sub>4</sub> and evaporated to give a liquid compound. The product is purified by flash chromatography



(eluent: EtOAc (300 ml)). 0.09 g, 33%, of a colourless liquid product (compound 30) is obtained.

\*  $^1\text{H}$  NMR (200.13 MHz,  $\text{CDCl}_3/\text{CHCl}_3$ : 7.24 ppm/TMS):  
 5  $\delta(\text{ppm})=8.6$  (m, 2H,  $\text{NHCO}$ ); 7.23-7.6 (m, 4H, Ph-H); 6.2 (m, 1H, NH); 4.23 (m, 2H,  $\text{H}_8$ ); 2.9-3.2 (m, 3H,  $\text{H}_\alpha$ ,  $\text{H}_\epsilon$ ,  $\text{H}_\delta$ ); 2.1 (s, 3H, N- $\text{CH}_3$ ); 2.3 (s, 3H, Ph- $\text{CH}_3$ ); 1.89 (m, 4H,  $\text{H}_{6\beta}$ ,  $\text{H}_{7\beta}$ ,  $\text{H}_{\alpha'}$ ); 1.3-1.6 (m, 3H,  $\text{H}_{4\alpha}$ ,  $\text{H}_{6\alpha}$ ,  $\text{H}_{7\alpha}$ ); 1.35 (m, 9H,  $(\text{CH}_3)_3$ ); 1.03-1.21 (m, 11H,  $\text{H}_2$ ,  $\text{H}_\beta$ ,  $\text{H}_{\beta'}$ ,  $\text{H}_\delta$ ,  $\text{H}_\gamma$ ,  $\text{H}_{\gamma'}$ ).

\*  $^{13}\text{C}$  NMR (50.2 MHz,  $\text{CDCl}_3/\text{CHCl}_3$ : 77 ppm/TMS):  
 $\delta(\text{ppm})=169.6$  ( $\text{NHCO}$ ): 168.03 ( $\text{NHCO}$ ); 156.73 ( $2\times\text{COOC}(\text{CH}_3)_3$ ); 141.76 ( $\text{C}_{4'}$ ); 128.42 ( $\text{C}_{4'}$ ); 126.22 and 125.90 ( $\text{C}_{3'}$ ,  $\text{C}_{5'}$ ); 117.86 ( $\text{C}_{3'}$ ); 79.43 ( $2\times\text{C}(\text{CH}_3)_3$ ); 75.79  
 15 ( $\text{C}_4$ ); 62.07 ( $\text{C}_5$ ); 54.03 ( $\text{C}_\alpha$ ); 49.59 ( $\text{C}_2$ ); 41.55 ( $\text{NHCHH}_3$ ); 40.40 ( $\text{C}_8'$ ); 39.70 ( $\text{C}_\epsilon$ ); 34.11 ( $\text{C}_4$ ); 31.43 ( $\text{C}_\epsilon$ ); 29.99 ( $\text{C}_\gamma$ ); 29.64 ( $(\text{CH}_3)_3$ ); 28.78 ( $\text{C}_6$ ); 26.52 ( $\text{C}_{\beta'}$ ); 22.54 ( $\text{C}_\beta$ ); 22.40 (Ph- $\text{CH}_3$ ).

20 \* Infrared

1689  $\text{cm}^{-1}$ :  $\nu(\text{NHCOO})$ ; 1678  $\text{cm}^{-1}$ :  $\nu(\text{NHCO})$

\* Mass spectrum

The molar mass 4 is 657.

25 Peak 658 corresponds to  $(\text{M}+\text{H})$ .

F) EXAMPLES OF STEPS FOR DEPROTECTING THE XH FUNCTIONS AND FOR REACTING THESE DEPROTECTED FUNCTIONS WITH CS<sub>2</sub> TO FORM A BIS-DITHIOCARBAMATE STRUCTURE ACCORDING TO THE PROCESS OF THE PRESENT INVENTION

5 Example 25: Synthesis of N<sup>ε</sup>,N<sup>δ'</sup>-bis-dithiocarbamate)-  
(α',δ'-diaminobutyl)-N<sup>α</sup>(carboxybenzyloxy)-D-lysine:  
compound (31)

5 mg of compound (28) are dissolved in 500 μl of absolute methanol. 100 μl of trifluoroacetic acid are  
10 added. The mixture is stirred for 30 minutes. The mixture is evaporated under vacuum. When the reaction mixture is dry, 500 μl of methanol and 500 μl of piperidine are added. The mixture is left for a further 30 minutes. The reaction mixture is then evaporated to  
15 dryness under vacuum. 1 ml of methanol and 200 ml of carbon sulphide (CS<sub>2</sub>) are then added. The reaction mixture is stirred at room temperature for 2 hours and then evaporated to dryness. Compound (31) is maintained dry at -18°C.

20

Example 26: 2β-[N<sup>ε</sup>,N<sup>δ'</sup>-bis(dithiocarbamate)-(α',δ'-  
diaminobutyl)-D-lysine]-3β-(4'-tolyl)tropane: compound  
(32)

The process is performed in the same manner as  
25 Example 25, but with 5 mg of compound (30). The reaction mixture is stirred at room temperature for 2 hours and then evaporated to dryness. Compound (32) obtained is maintained dry at -18°C.

Example 27: The deprotection and synthesis of the bis-dithiocarbamates (non-functionalized complexing agents) of products (13), (14), (15), (16) and (17) obtained in the preceding examples leads to the corresponding compounds (34), (35), (36), (37) et (38)

10 mmol of each peptide are dissolved in 5 ml of absolute methanol. 5 ml of a 0.1M solution of piperidine in methanol are added and the mixture is stirred for 1 hour. The mixture is evaporated under vacuum.

The dry residue is taken up in 5 ml of methanol and 3 ml of carbon sulphide are added. The mixture is stirred for 2 hours. The reaction mixture is evaporated to dryness and is stored at -18°C.

15

Example 28: Deprotection and synthesis of the bis-dithiocarbamates (substituted with a tropane derivative) of products (18), (19), (20) and (21) obtained in the preceding examples leads to compounds (44), (45), (46) and (47)

The process is performed in the same manner as in Example 27, but with the products (18), (19), (20) and (21). Compounds (44), (45), (46) and (47) are obtained.

25

#### **G) RADIOLABELLING OF COMPOUNDS ACCORDING TO THE INVENTION**

Example 29: The radiolabelling of products (31), (34), (35), (36), (37) and (38) with TcN leads to compounds (33), (39), (40), (41), (42) and (43)

30

Synthesis of the TcN intermediate

100  $\mu$ g of tin chloride, 5 mg of SDH (succinyl dihydrazide) and 5 mg of PDTA (1,2-propanediamino-N,N,N',N'-tetraacetic acid) were freeze-dried in a labelling flask. 3 ml of  $\text{TcO}_4^-$  (60 mCi) are added to this lyophilizate. The mixture is left to act for 15 minutes.

Complexation:

2 mg of bis-dithiocarbamate in 1 ml of ethanol are added to 1 ml of TcN. The mixture is left to react for one hour. The reaction is analysed by HPLC (reverse-phase, methanol-water). Labelling yield >95%.

The radiolabelling of compound 38 showed that the radiolabelled molecule, isolated by HPLC and left at room temperature, was stable for more than 4 hours.

15

Example 29a: Radiolabelling of products (31), (34), (35), (36), (37) and (38) with copper-64

2 mg of bis-dithiocarbamate (products 31, 34, 35, 36, 37 or 38) in 0.5 ml of ethanol are added to 1 ml of 0.1 M pH 5.5 ammonium acetate buffer containing 2 mCi of  $^{64}\text{Cu}$ -acetate. The mixture is left to act for one hour. The reaction is analysed by HPLC (reverse-phase, methanol-water).

The labelling yield is greater than 95% for each of the products.

Example 30: Radiolabelling of products (32), (44), (46) and (47) with TcN leads to products (48), (49), (50), (51) and (52)

The process is performed in the same manner as in Example 29, but with products (32), (44), (45), (46)

and (47). Products (48), (49), (50), (51) and (52) are obtained.

Example 30a: Radiolabelling of products (32), (44), (46) and (47) with copper-64 leads to products (48), (49), (50), (51) and (52)

The process is performed in the same manner as in Example 29a, but with products (32), (44), (45), (46) and (47).

The labelling yield is greater than 95% for each of the products.

#### H) EXAMPLES OF THE USE OF THE COMPOUND OF THE PRESENT INVENTION

Example 31: Bioavailability of Lys-Lys bis-dithiocarbamate in rats

The molecule was radiolabelled as described in Example (29). The radiolabelled compound is then isolated by HPLC, evaporated and taken up in 0.9% saline medium. The bioavailability in rats gives the following results (see Table 1):

- time 30 minutes and 60 minutes: 3 animals per point,
- time 3 hours: 2 animals per point,
- time 24 hours: 1 animal per point.

The results are expressed as a percentage of dose injected per organ.

The rats' urine was collected 1 hour 30 minutes after injection and analysed by HPLC. The result of this analysis is 87% of unchanged complex.

Table 1

Organs	Average 30 min	Average 1 h	Average 3 h	Average 24 h
blood	0.67	0.34	0.20	0.11
liver	14.38	9.08	3.84	1.33
kidneys	4.55	4.18	3.87	2.65
adrenals	0.02	0.01	0.01	0.00
spleen	0.13	0.09	0.05	0.04
lungs	0.43	0.28	0.15	0.08
heart	0.21	0.10	0.06	0.03
bladder	0.47	0.32	0.05	0.01
urine	14.39	14.70	0.44	0.05
stomach	8.24	3.36	2.64	0.08
intestine	20.55	32.92	51.4	0.49
caecum	0.31	0.18	0.11	0.66
colon	0.46	0.23	0.19	0.87
brain	0.03	0.01	0.01	0.01

5 Example 32: Biological results of compounds (48) and products (50), (51) and (52)

The model chosen is the rat. Depending on the compounds, we performed one or two sacrifice times (30 minutes or 1 hour).

10 At the times chosen, the brains were removed and the areas of interest were isolated and counted. From these results, we deduced the following:

- the crossing of the blood-brain barrier by the compound under consideration,
- 15 - a striatum/cerebellum ratio.

Table II below collates the results of this experiment.

Table II

TcN tropane-bis-dithiocarbamate approach

Product	Precursor	Biological results		
		Biodistribution	S/C	Kapp
50	2 $\beta$ -[N <sup>ε</sup> ,N <sup>ε</sup> -bis(dithiocarbamate)-N-(5-aminohexanoyl)lysinyloxymethyl]-3 $\beta$ -(4'-tolyl)tropane n=4 m=3	30': cerebellum: 0.168% striatum: 0.167% crossing of blood-brain barrier: 0.483%	1.00	
		1 h: cerebellum: 0.077% striatum: 0.075% crossing of blood-brain barrier: 0.217%	0.97	
51	2 $\beta$ -[N <sup>δ</sup> ,N <sup>ε</sup> -bis(dithiocarbamate)-N-(5-aminohexanoyl)ornithyloxymethyl]-3 $\beta$ -(4'-tolyl)tropane n=3 m=4	30': cerebellum: 0.113% striatum: 0.126% crossing of blood-brain barrier: 0.344%	1.11	
		1 h: cerebellum: 0.069% striatum: 0.071% crossing of blood-brain barrier: 0.200%	1.03	
52	2 $\beta$ -[N <sup>ε</sup> ,N <sup>δ</sup> -bis(dithiocarbamate)-N-(5-aminopentanoyl)lysinyloxymethyl]-3 $\beta$ -(4'-tolyl)tropane n=4 m=4	30': cerebellum: 0.114% striatum: 0.133% crossing of blood-brain barrier: 0.358%	1.17	
		1 h: cerebellum: 0.065% striatum: 0.064% crossing of blood-brain barrier: 0.182%	0.98	





present invention on residues 15-16 is thus obtained in freeze-dried form.

5     Example 34: Radiolabelling of product (53) with technetium

      A flask containing a lyophilizate of product (53) is taken up in 1 ml of injection-grade water. 0.5 ml of  $\text{TcO}_4^-$  (20 mCi) is added to this solution. After 30 minutes, 0.2 mg of bis-dithiocarbamate (product 53) in a 0.5 M pH 7.4 phosphate buffer and optionally ethanol to dissolve the mixture are added. The manipulation is left to react for 1 hour.

      PRC analysis is performed by HPLC. The labelling yield for compound 54 is greater than 95%.

15

Example 35: Reaction of carbon sulphide with a monoclonal antibody (ACM) (product 55)

      5 mg of antibody (anti-ACE) are dissolved in 3 ml of injection-grade water. 400  $\mu\text{l}$  of carbon sulphide are added. The mixture is left stirring at 4°C for 4 hours. After this time, the  $\text{CS}_2$  is removed under vacuum at room temperature (the volume is brought to 3 ml). Product (55) is stored in solution at -18°C.

25     Example 36: Radiolabelling of the modified antibody (product 56) with technetium

      Synthesis of the TCN intermediate

      100  $\mu\text{g}$  of tin chloride, 5 mg of SDH (succinyl dihydrazide) and 5 mg of PDTA (1,2-propanediamino-N,N,N',N'-tetraacetic acid) were freeze-dried in a labelling flask. 3 ml of  $\text{TcO}_4^-$  (60 mCi) are added to

30

this lyophilizate. This reagent is left to act for 15 minutes.

1.5 mg of antibody (1 ml) and 1.5 ml of TcN (30 mCi) are placed in a labelling flask. The mixture  
5 is left at room temperature for 1 hour. The labelling yield is checked by paper chromatography. Labelling yield for compound (56) is 93%.

Example 37: Formulation of a diagnostic kit

10       Flask 1: 100  $\mu$ g of tin chloride, 5 mg of SDH (succinyl dihydrazide) and 5 mg of PDTA (1,2-propanediamino-N,N,N',N'-tetraacetic acid) were freeze-dried.

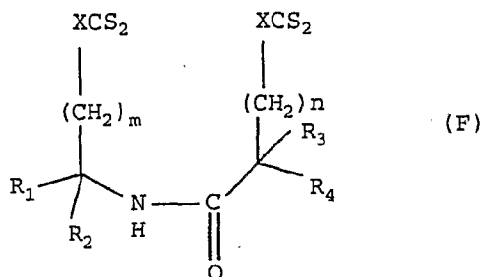
          Flask 2: 2 mg of bis-dithiocarbamate (more specifically chelation complex according to the  
15 invention, containing two dithiocarbamate functions) are packaged in 1 ml of injection-grade water.

          Preparation: 3 ml of TcO<sub>4</sub> (60 mCi) are added to flask 1. This reagent is left to act for 15 minutes and 1 ml of this solution is added to flask 2. This  
20 solution is left to act for one hour. The radiolabelling is ready for injection. Labelling yield  $\geq 95\%$ .

          The reaction is analysed by HPLC (reverse-phase, methanol-water).

## CLAIMS

1. Compound for chelating a metal or a metal complex, characterized in that it consists of a bis-dithiocarbamate structure (F) having the following formula:



in which n and m are integers such that  $5 \leq m+n \leq 10$ ,

X is chosen independently from S and NH,

10  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$  and  $\text{R}_4$  are chosen independently from H and an organic function chosen from  $-\text{COOR}_5$ ,  $\text{NR}_5\text{R}_6$  and  $-\text{CH}_2\text{OR}_5$  in which  $\text{R}_5$  and  $\text{R}_6$ , when it is present, are chosen independently from a hydrogen; an amino acid; a peptide; a protein; an organic function; a group chosen

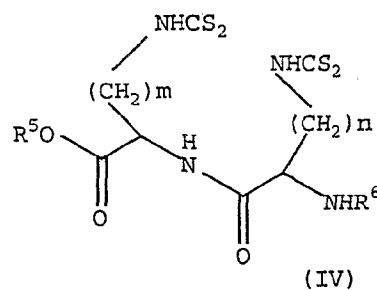
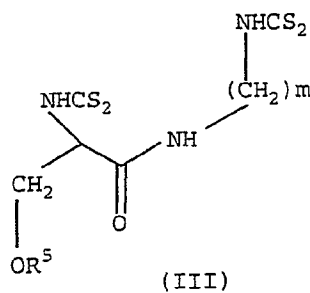
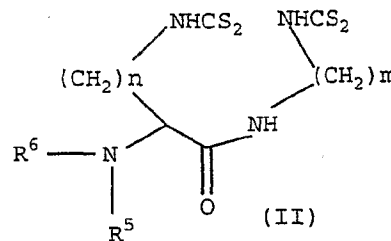
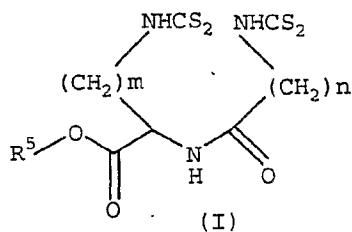
15 from alkoxycarbonyl or aryloxycarbonyl ( $-\text{COOR}^7$ ), carboxyl ( $-\text{COOH}$ ), acyloxy ( $-\text{O}_2\text{R}^7$ ), carbamoyl ( $-\text{CONR}^7$ ), cyano ( $-\text{CN}$ ), alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, arylalkylcarbonyl, hydroxyl ( $-\text{OH}$ ), amino ( $\text{NR}^7$ ), halogen, allyl, alkoxy ( $-\text{OR}^7$ ), S-alkyl and

20 S-aryl,  $\text{R}^7$  representing a  $\text{C}_1$  to  $\text{C}_{10}$  alkyl or aryl group; an organic molecule chosen from (i) an optionally substituted alkyl, acyl, aryl or alkyne group, (ii) a saturated or unsaturated, optionally substituted or aromatic carbon-based ring or (iii) a saturated or

25 unsaturated, optionally substituted or aromatic heterocycle, these groups and rings (i), (ii) and (iii) possibly being substituted with substituted phenyl

groups, substituted aromatic groups or alkoxycarbonyl or aryloxy carbonyl ( $-\text{COOR}^8$ ), carboxyl ( $-\text{COOH}$ ), acyloxy ( $-\text{O}_2\text{R}^8$ ), carbamoyl ( $-\text{CONR}^8$ ), alkylcarbonyl, alkylarylcarbonyl, arylcarbonyl, arylalkylcarbonyl, hydroxyl ( $-\text{OH}$ ), amino ( $\text{NR}^8$ ), halogen, allyl, alkoxy ( $-\text{OR}^8$ ), S-alkyl or S-aryl groups,  $\text{R}^8$  representing a  $\text{C}_1$  to  $\text{C}_{10}$  alkyl or aryl group; a monoclonal antibody; a hormone; and a pharmaceutically acceptable vector.

2. Chelation compound according to Claim 1, in which the bis-dithiocarbamate structure consists of a structure whose formula is chosen from formulae (I), (II), (III) and (IV) below:



in which  $\text{R}^5$ ,  $\text{R}^6$ ,  $n$  and  $m$ , when they are present, are as defined in Claim 1.

3. Compound according to Claim 1 or 2, in which m and n are independently 3, 4 or 5.

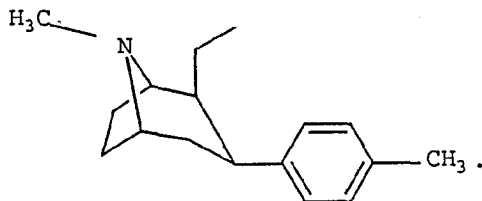
4. Compound according to Claim 2 or 3, in which  
5  $R^5 = H$ .

5. Compound according to Claim 2 or 3, in which  
 $R^5 = CH_3$ .

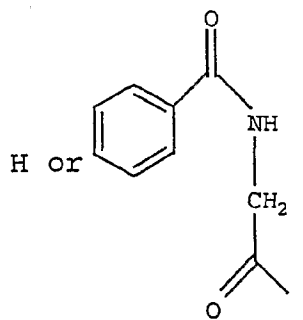
10 6. Compound according to Claim 2 or 3, in which  $R^5$  is a tropane derivative.

7. Compound according to Claim 2 or 3, in which  $R^5$  has the following formula:

15



8. Compound according to Claim 1, consisting of a structure of formula (F) in which  $R^1$ ,  $R^3$  and  $R^4 = H$  and  
20  $R^2$  is  $NR^5R^6$ , in which  $R^5 = H$  and  $R^6$  is chosen from:



9. Chelation product consisting of a chelation compound according to any one of Claims 1 to 8 and of a metal or a metal complex.

5

10. Chelation product according to Claim 9, in which the metal is copper or an isotope thereof.

11. Chelation product according to Claim 9, in  
10 which the metal is chosen from a transition metal.

12. Chelation product according to Claim 9, in which the metal complex is TcN or ReN.

15 13. Use of a chelation compound according to any one of Claims 1 to 8, for manufacturing a medicinal product or a diagnostic product.

14. Use of a chelation compound according to any  
20 one of Claims 1 to 8, for manufacturing a radiopharmaceutical for therapy or for diagnosis.

15. Use of a chelation compound according to any one of Claims 1 to 8, for manufacturing a  
25 radiopharmaceutical for visualizing the uptake of dopamine or serotonin.

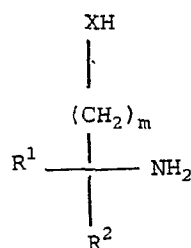
16. Use of a chelation product according to any one of Claims 9 to 12, for manufacturing a medicinal  
30 product or a diagnostic product.

17. Use of a chelation product according to any one of Claims 9 to 12, for manufacturing a radiopharmaceutical for therapy or diagnosis.

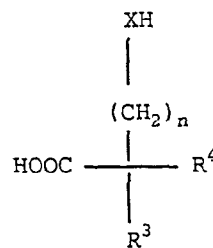
5 18. Use of a chelation product according to any one of Claims 9 to 12, for manufacturing a radiopharmaceutical for visualizing the uptake of dopamine or serotonin.

10 19. Process for manufacturing a bis-dithiocarbamate structure as defined in Claim 1, comprising, successively:

- a step of protecting the XH functions of the compounds of formulae (V) and (VI) below:



(V)



(VI)

15

in which  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ , X, m and n are as defined in Claim 1,

- a step of activating the  $-\text{COOH}$  function of compound (VI),

20

- a step of linking the compound of formula (V) and compound (VI) via the activated carboxyl function of compound (VI),

- a step of deprotecting the XH functions, and

25 - a step of reacting the deprotected XH functions with  $\text{CS}_2$  to form a bis-dithiocarbamate structure according to Claim 1.

20. Process for manufacturing a structure according to Claim 1 or 2, comprising a process according to Claim 19 for manufacturing a bis-dithiocarbamate structure, and also comprising a step of  
5 attaching a radical  $R^5$  and optionally  $R^6$  to this bis-dithiocarbamate structure or to an intermediate product in its manufacture to obtain a chelation compound according to Claim 1 or 2.

10

21. Process for manufacturing a structure as defined in Claim 1 or 2, comprising:

- a step of reacting two  $\epsilon$ - $NH_2$  functions of two contiguous amino acids of a precursor molecule  
15 of the structure according to Claim 1 or 2 with  $CS_2$  so as to form a structure according to Claim 1 or 2,

the precursor molecule constituting the radical  $R^5$  and optionally the radical  $R^6$ .

20

22. Process for preparing a chelation product as defined in Claim 9, comprising the manufacture of a bis-dithiocarbamate structure defined in Claim 1 or 2 according to a manufacturing process defined in  
25 Claim 20 or 21, and a reaction for complexing a metal or a metal complex via the said bis-dithiocarbamate structure manufactured.

23. Process according to Claim 22, in which the  
30 metal is a transition metal.



24. Process according to Claim 22, in which the metal is copper.

25. Process according to Claim 22, in which the  
5 metal complex is TcN or ReN.

26. Diagnostic kit comprising a chelating compound according to any one of Claims 1 to 8.